Norwegian Cardiovascular Disease Model (NorCaD) – a simulation model for estimating health benefits and cost consequences of cardiovascular interventions

Report from Kunnskapssenteret (Norwegian Knowledge Centre for the Health Services)
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Background: Cardiovascular disease (CVD) is the most frequent cause of death in all developed countries and most other as well. In Norway, about 40% of all deaths are attributed to CVD and the population life expectancy would increase by about 4 years if all CVD were eliminated. A range of new interventions has been proposed, and several are in use. The development of new interventions continues, but not all improvements have a substantially increased effect compared with older treatments, and some are costly. In Norway, the Patients' Right Act grants patients the right to treatment, but only if the costs are reasonable in relation to the health benefits. It is therefore a need to quantify costs and benefits of CVD interventions. **Method:** We used the software program TreeAge Pro to develop a transition model (Markov model) with cycles of one year from the age of 30 years to death or the age of 100. The model starts with all individuals free from symptoms of cardiovascular disease. All individuals are at risk of having one or more of the following primary CVD events: acute myocardial infarction (AMI), stroke, angina pectoris or heart failure. The risks of these *(continued)*

Norwegian Knowledge Centre for the Health Services (Kunnskapssenteret)
PO Box 7004, St. Olavs plass
N-0130 Oslo
(+47) 23 25 50 00
www.kunnskapssenteret.no
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(continued from page one) events are as far as possible based on population data from Norwegian registries. After an event, patients move to one of the following health states: asymptomatic CVD (post CVD), heart failure and stroke sequelae. While patients are in any of these states, they are at risk of secondary CVD events. **Discussion:** The NorCaD model was designed for economic evaluation of primary CVD prevention, but can also be used for secondary prevention. The model is comprehensive in terms of potential events and health states, but is created for a Norwegian setting. The model's strength is its complexity and ability to analyse a wide range of interventions. Such abilities require a wide range of input data. In total the model has about 200 parameters each with its own uncertainty. By modelling and quantifying costs and outcomes, the uncertainties become explicit. **Conclusion:** The NorCaD model is a comprehensive and validated decision-analytic model which has potential to be used in several settings related to cardiovascular disease in Norway and elsewhere.

Title	Norwegian Cardiovascular Disease Model (NorCaD) – a simulation model for estimating health benefits and cost consequences of cardiovascular interventions
Institution	Norwegian Knowledge Centre for the Health Services (NOKC) John-Arne Røttingen, *Director*
Authors	Torbjørn Wisløff, *researcher* (project leader) Randi M. Selmer, *senior researcher* Sigrun Halvorsen, *head cardiologist* Ivar Sønbø Kristiansen, *professor*
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Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Directorate for Health and Social Affairs, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

Norwegian Knowledge Centre for the Health Services
Oslo, October 2008

1-side oppsummering

Norwegian Cardiovascular Disease Model (NorCaD)
– en simuleringsmodell for estimering av helse og kostnader relatert til hjerte- og karsykdom

NorCaD-modellen (Norwegian Cardiovascular Disease model) er en simuleringsmodell som følger grupper av individer fra de er friske til de får hjerte- og karsykdom og senere dør. Individene starter som friske, men kan bli utsatt for hjerte- og karhendelser (hjerteinfarkt, hjerneslag mv) og gå over i kroniske tilstander som død, hjertesvikt eller følgetilstand av slag. Modellen anvendes for å evaluere tiltak mot hjerte- og karsykdom. Den er basert på norske tall for risiko for hjerte- og karsykdommer, samt internasjonal litteratur når det gjelder senere forløp av sykdommen samt effekt av forebyggings- eller behandlingstiltak.

Modellen fanger opp de kostnader det norske helsevesenet påføres som følge av hjerte- og karsykdom. Her er behandlingsrutiner basert på ekspertvurderinger og retningslinjer mens enhetskostnader er innhentet fra diverse norske offisielle kilder. Modellen opererer med tidssykluser på ett år, og individer kan følges fra 30 til 100–års alder (eller død).

Modellen fanger opp kostnader, livskvalitet og leveår etter hvert som hjerte- og karsykdommene utvikler seg over tid. Modellen kan brukes til økonomisk evaluering av en rekke ulike tiltak mot hjerte- og karsykdom ved at den beregner kostnad per vunnet leveår eller kostnad per kvalitetsjustert vunnet leveår.

Sammendrag

BAKGRUNN

Hjerte- og karsykdom er vanligste dødsårsak i alle industrialiserte land og i de fleste andre land. I Norge er omtrent 40 % av alle dødsfall relatert til hjerte- og karsykdom, og levealderen vil øke med ca. 4 år hvis all hjerte- og karsykdom helt ble eliminert. I mange år har leger, forskere, legemiddelfirmaer, myndigheter og andre arbeidet for å redusere forekomsten av hjerte- og karsykdom. En rekke nye tiltak har blitt foreslått, og mange av disse er i utstrakt bruk. Utvikling av nye tiltak fortsetter, men ikke alle nyvinninger gir betydelig mereffekt sammenlignet med tidligere behandlingsmetoder, og noen er svært kostbare. I Norge gir Pasientrettighetsloven pasienter rett til behandling, men bare hvis kostnadene står i et rimelig forhold til effektene. Det er derfor behov for å tallfeste effekter og kostnader av tiltak mot hjerte- og karsykdom.

Formålet med dette prosjektet var å lage en modell for utvikling av aterosklerotisk hjerte- og karsykdom fra asymptomatisk tilstand, via diverse hjerte- og karhendelser, til død, og underveis registrere leveår, livskvalitet og kostnader.

METODE

Vi brukte dataprogrammet TreeAge Pro for å utvikle en transisjonsmodell (Markovmodell) med ett-årssykluser fra alder 30 år til alle er døde eller fylt 100 år. Modellen starter med alle individer i en tilstand uten symptomer på hjerte- og karsykdom. Alle individer har til enhver tid risiko for å utvikle en eller flere primære hjerte- og karhendelser; akutt hjerteinfarkt, hjerneslag, angina pectoris eller hjertesvikt. Risikoen for disse hendelsene er hentet fra norske helseregistre så langt det har vært mulig. Etter hver hendelse flyttes pasientene over i en ny helsetilstand: asymptomatisk hjerte- og karsykdom, hjertesvikt, slagsekvele og død. Når pasientene er i disse tilstander (med unntak av død), har de risiko for å utvikle sekundære hjerte- og karlidelser.

Risikodata for sekundære hjerte- og karhendelser er hentet både fra internasjonale dataregistre (primært europeiske) og fra en rekke randomiserte kliniske studier. Da slike studier ofte ekskluderer de sykeste pasientene, har vi justert risikotallene slik at de skal representere gjennomsnittspasienter.

En Markovmodell har ikke innebygd minne om tidligere sykehistorie. For noen helsetilstander er det imidlertid rimelig å anta at tidligere sykehistorie påvirker sannsynligheten for nye hendelser. Vi har derfor delt noen helsetilstander (asymptomatisk, slagsekvele og hjertesvikt) inn i flere tilstander for å fange oppforskjellig risiko. Vi delte også helsetilstanden død inn i ”død av hjerte- og karsykdommer” og ”død av andre årsaker”.

Effekten av intervensjoner (livsstilsendringer, medikamenter, etc.) øker levealderen ved å redusere risikoen for hjerte- og karhendelser og død. Dette skjer i modellen ved å justere risikotallene med en faktor (relativ risikoreduksjon). Disse faktorene vil oftest stamme fra systematiske oversikter over intervensjonseffekter.

Alle kostnader relatert til hjerte- og karhendelser eller -tilstander fanges opp etter hvert som sykdommen utvikler seg. Data for ressursforbruk ved hendelser og tilstander er basert på ekspertvurderinger og til en viss grad på norske publiserte data. Enhetskostnader er basert på offisielle norske kilder der de finnes tilgjengelig.

Modellen uttrykker helsegevinster som vunne leveår. I den grad beslutningstagere etterspør data på livskvalitet, kan man tilordne livskvalitetsvekter til de forskjellige helsetilstander og uttrykke helsegevinster som kvalitetsjusterte leveår. Modellen er tilrettelagt for såkalt probabilistisk sensitivitetsanalyse.

VALIDERING OG RESULTATER

Vi validerte NorCaD-modellen ved å sammenligne forventet levealder i modellen med levealder i befolkningen. Modellen viste forventet gjenstående levealder som avvek mindre enn 1 % fra tallene fra Statistisk sentralbyrå.

DISKUSJON

NorCaD-modellen er designet for økonomisk evaluering av primærforebyggende tiltak mot hjerte- og karsykdom, men kan også brukes til sekundærprevensjon. Modellen er omfattende med tanke på potensielle hendelser og tilstander sammenlignet med andre liknende modeller. Den er laget for en norsk setting, primært med et helsetjenesteperspektiv. Modellens styrke er dens kompleksitet og evne til å analysere et bredt spektrum av tiltak. Modellens svakhet er usikkerheten i mange av inputdataene. Totalt inneholder modellen over 200 parametre, hver med sin egen usikkerhet. Modellen gir imidlertid gode muligheter for å analysere konsekvensene av usikkerheten, og å gi veiledning om hvilke studier som er mest egnet til å redusere usikkerheten. Det er dessuten viktig å poengtere at enhver beslutning om tiltak mot hjerte- og karsykdom er basert på minst like usikker informasjon som modellen bygger på. Modelleringen av sykdomsforløpet med registrering av helseutfall og kostnader underveis er med på å gjøre usikkerhetene mer eksplisitt.

Modellen er basert på nyere norske insidenstall, og dette anser vi som er en stor fordel sammenlignet med å bruke eldre data fra Framinghamstudien i USA.

KONKLUSJON

NorCaD-modellen er en omfattende simuleringsmodell som kan brukes for økonomisk evaluering av en rekke ulike tiltak mot hjerte- og karsykdom. Modellen kan således være et vik-

tig hjelpemiddel når helsemyndighetene skal treffe beslutning om forebygging og behandling av hjerte- og karsykdom.

Key messages

Norwegian Cardiovascular Disease Model (NorCaD)
– a simulation model for estimating health benefits and cost consequences of cardiovascular interventions

This report provides an introduction to the NorCaD cardiovascular model. The model was constructed for use in health technology assessments (HTAs) of prevention strategies directed towards cardiovascular disease. NorCaD is a state transition model which follows individuals from before they have any symptoms of cardiovascular disease until death.

- The model is based on Norwegian data on incidence of primary cardiovascular events and adapted to a Norwegian health care setting.
- Probabilities of disease progression are to a large extent based on data from international registries and randomised trials.
- Unit costs are gathered from Norwegian official data and resource use is mainly based on expert opinion.
- The model has a cycle length of one year, and runs from age 30 to 100 or to death.

As the cardiovascular disease progresses, costs, quality of life and life years are recorded to give the opportunity of cost-effectiveness-analyses.

The model is validated to fit Norwegian mortality data as close as possible. However there are still limitations regarding the model.

Executive summary

Norwegian Cardiovascular Disease Model (NorCaD)
– a simulation model for estimating health benefits and cost consequences of cardiovascular interventions

BACKGROUND

Cardiovascular disease (CVD) is the most frequent cause of death in all developed countries and most other as well. In Norway, about 40% of all deaths are attributed to CVD and the population life expectancy would increase by about 4 years if all CVD were eliminated. For decade's doctors, researchers, pharmaceutical companies, governments and others have struggled to reduce the burden of CVD. A range of new interventions has been proposed, and several are in use. The development of new interventions continues, but not all improvements have a substantially increased effect compared with older treatments, and some are costly. In Norway, the Patients' Right Act grants patients the right to treatment, but only if the costs are reasonable in relation to the health benefits. It is therefore a need to quantify costs and benefits of CVD interventions.

The objective of the current project was to develop a model of atherosclerotic CVD from its asymptomatic stage through various CVD events and complications to death, and capture data on life years, quality of life and costs.

METHODS

We used the software program TreeAge Pro to develop a transition model (Markov model) with cycles of one year from the age of 30 years to death or the age of 100. The model starts with all individuals free from symptoms of cardiovascular disease. All individuals are at risk of having one or more of the following primary CVD events: acute myocardial infarction (AMI), stroke, angina pectoris or heart failure. The risks of these events are as far as possible based on population data from Norwegian registries. After an event, patients move to one of the following health states: asymptomatic CVD (post CVD), heart failure, stroke sequelae and death. While patients are in any of these states (except dead), they are at risk of secondary CVD events.

The risks of secondary cardiovascular events are based on data from both registries and a range of randomised trials. Because randomised trials usually include patients with less severe health profiles, we adjusted data from these randomised trials to better represent average patients.

A Markov model has no built-in memory of previous disease-history. In some health states, however, it is reasonable to assume that previous disease history affects the probability of new events. To overcome this problem, we divided some health states (asymptomatic, stroke

sequelae and heart failure) into more health states to capture differential risks. We also divided the health state dead into death from CVD and death from other causes to account for causes of death.

The effect of interventions increases life expectancy by the reduced risk of cardiovascular events and death. In the model these effects are relative risk reductions which are based on systematic reviews of interventional effects.

All costs related to CVD events or states are recorded as the disease progresses. Data on unit costs were taken from official Norwegian sources where possible. Data on resource use was to a large extent based on expert opinion, and to some extent on published data.

The model measures health outcome as life years based on the mortality risks built into it. To the extent decision makers request data on quality adjusted life years, the model allows for such outcome by assigning quality weights to the different health states.

VALIDATION

We validated the NorCaD model by fitting model survival to survival in the Norwegian population. After validation, the model gave expected remaining lifetime less than 1% away from predictions by Statistics Norway.

DISCUSSION

The NorCaD model was designed for economic evaluation of primary CVD prevention, but can also be used for secondary prevention. The model is comprehensive in terms of potential events and health states, but is created for a Norwegian setting. The strength of the model is its complexity and ability to analyse a wide range of interventions. Such abilities, however, require a wide range of input data. In total the model has about 200 parameters each with its own uncertainty. It should be noted, however, that any decision on CVD intervention is implicitly based on such uncertain information. By modelling and quantifying costs and outcomes, the uncertainties become explicit.

The model is based on recent Norwegian incidence data, which is an advantage compared to the conventional use of Framingham data that are older and taken from another country (USA).

CONCLUSION

The NorCaD model is a comprehensive and validated decision-analytic model which has potential to be used in several settings related to cardiovascular disease in Norway and elsewhere.

ABOUT US

Norwegian Knowledge Centre for the Health Services summarizes and disseminates evidence concerning the effect of treatments, methods, and interventions in health services, in addition to monitoring health service quality. Our goal is to support good decision making in order to provide patients in Norway with the best possible care. The Centre is organized under The Directorate for Health and Social Affairs, but is scientifically and professionally independent. The Centre has no authority to develop health policy or responsibility to implement policies.

Norwegian Knowledge Centre for the Health Services
PB 7004 St. Olavs plass
N-0130 Oslo, Norway
Telephone: +47 23 25 50 00
E-mail: post@kunnskapssenteret.no
Full report (pdf): www.kunnskapssenteret.no

Contents

Foreword

This project was initiated by the researchers Ivar Sønbø Kristiansen and Torbjørn Wisløff at the former Norwegian Centre for Health Technology Assessment (now a part of NOKC). The idea was to construct a model which could be used in several types of economic evaluations of cardiovascular interventions, primary as well as secondary ones.

The project group has consisted of the following persons:

- Project coordinator: researcher Torbjørn Wisløff, Norwegian Knowledge centre for the health services (NOKC)
- Senior researcher, dr.philos. Randi M. Selmer, Norwegian Institute of Public Health
- Head cardiologist, dr.med. Sigrun Halvorsen, Ullevål University Hospital
- Professor Ivar Sønbø Kristiansen (MD, PhD, MPH), University of Oslo and University of Southern Denmark

John-Arne Røttingen
Direktør

Marianne Klemp Gjertsen
Forskningsleder

Torbjørn Wisløff
Forsker, prosjektleder

1 Introduction

Cardiovascular disease (CVD) represents important costs in terms of health losses and use of health care resources. CVD is the most frequent cause of death in most countries and accounted for 35.5% of all mortality in 2006 in Norway (1). Considerable proportions of health care budgets are devoted to prevention and treatment of CVD. Life expectancy in Norway would increase by 3.79 years in female and 4.33 years in males if all CVD-related mortality could be avoided (2). A large proportion of CVD, however, is caused by atherosclerosis which is a process that starts early in life, even if the acute events in adult life may be induced by faster mechanisms such as thrombosis and haemorrhages. It is therefore unlikely that CVD can be totally avoided, but the underlying disease process (atherosclerosis) can be slowed and the disease consequences will be postponed accordingly.

Atherosclerosis is a multifactorial disease process, with age, sex, dyslipidaemia, hypertension, smoking and sedentary lifestyle as the most important risk factors (3). Interventions to postpone atherosclerosis or treat its complications include life style changes, pharmaceuticals, and revascularisation such as surgery and percutaneous coronary interventions (PCI). Even though health care budgets have been rapidly increasing in Norway, the demand for medical treatment is greater than health care budgets can meet. Society therefore needs to set priorities. This means that society might need to deny some patients treatment on the grounds that the resources could yield greater health benefits in other patients. Economic evaluation is a research tool that aims to quantify health benefits and costs of different medical interventions in order to guide priority setting.

Economic evaluation can be undertaken in randomised clinical trials in which costs and health consequences are captured and quantified. Because the results of economic evaluation are context specific in terms of country as well as patient groups, use of randomised trials as the sole basis for economic evaluation is not feasible. Evaluation is therefore typically performed within a simulation model. In this paper, we describe the logic, construction and data input (”parameter values”) of a cardiovascular model for Norway. In principle the model will allow evaluation of any kind of intervention aimed to prevent or treat CVD. Because CVD is a

chronic disease with recurring events and health states, the time dimension is crucial. Consequently, we chose to use a state transition model (Markov model) (4).

Modelling the course of CVD is not straightforward because:

- It is complicated to account for all CVD risk factors
- There may be interactions among risk factors (see section 2.4)
- The number of adverse events and consequent health states is large, especially if combination of health states (*e.g.* stroke sequelae and angina) shall be captured in the model

The challenge lies in capturing enough details to be realistic and avoiding details for which there are no data. With modern computer programs, the limitations of modelling lies more in lack of data than capacity to account for many events, health states and combination of health states.

1.1 ECONOMIC EVALUATION

Economics is based on the premise that resources should be spent such that they generate the maximum expected welfare or utility to the greatest number of people. If it is assumed that the objective of the health care system is to maximise health (measured as life years or quality adjusted life years), resource constraints means that resources should be allocated to activities that generate the greatest health benefits in relation to the amount of resources these activities require.

The measure of cost-effectiveness is based on the ratio of the incremental cost to the incremental effectiveness of the different interventions. Comparisons between different diseases require a standard outcomes measure that can be applied to all diseases. Life years gained is widely used, but this measure does not account for the difference in quality of life. Some interventions do not affect mortality, and their potential benefits will therefore not be captured if life year gained is applied as the sole measure of effectiveness. Quality adjusted life years (QALYs) were developed in order to overcome this problem. However one should be aware of the many different ways of measuring QALYs and that different methods yield different results (5).

A decision model usually starts with a decision node with two or more possible strategies (interventions, treatment arms). In each arm, the clinical course of events is modelled as close to real life as necessary. Because the clinical life of patients can be both very variable and very complex, we have to make simplifications. The most common and obvious simplification, is to not model things that will be equal in both/all arms. Other reasons for skipping certain elements might be that the addition/subtraction of this aspect does not alter the results in any significant way.

When modelling chronic diseases a Markov model or a discrete event simulation model can be placed inside the decision tree. A Markov model is a state transition model with fixed cycle length (for example one year). Hence, at the end of each cycle, the patients move from one health state to another or remains in the same. During the cycle, each patient might be subject to various events which might subsequently "move" the patient into another health state (*e.g.* an acute myocardial infarction (AMI) may move a patient from the health state disease-free to the health state congestive heart failure). Because Markov models themselves are without memory, one has to be careful when using this kind of model. If an event (except aging) causes a permanent change in probabilities of new events, then the easiest and most understandable solution, is to model this as a new health state. If this leads to an unwieldy number of health states, discrete event simulation might be an alternative (6, 7).

In every economic evaluation, there is uncertainty with respect to the parameter values. To inform the decision maker about this uncertainty, several types of sensitivity analyses can be conducted. A common approach is one-way sensitivity analyses, where each parameter is varied within reasonable bounds (*e.g.* 95% confidence intervals). In some cases it might also be appropriate to conduct two- and three-way sensitivity analyses. To explore the overall uncertainty (and also if the economic evaluation is going to lead to recommendations on further research) probabilistic sensitivity analyses are often conducted (8). This is mostly conducted as a Monte Carlo simulation of the "reasonable bounds" for all uncertain input parameters. More about sensitivity analyses is in section 2.11.

The area of cardiovascular disease modelling is far from new, and some earlier models are briefly presented below:

- The model from Berto and co-workers starts with healthy individuals and model their life until different coronary heart diseases or death by other causes (9). This model does not go any further after the first CHD event.
- CDC (Centers for disease control and prevention) diabetes cost-effectiveness group made a Markov model which models whether an individual gets CHD or continues to stay "normal" (10). In contrary to *e.g.* Berto's model, this model doesn't stop at first event, but also models that one can stay in the health states "angina" and "history of CA/MI" for several years.
- Huse and co-workers have, as CDC, modelled up to all individuals are dead (11). This is however a model which evaluates the difference between different statins. In this model it is possible to start and stop giving medications during the process, which is rather uncommon for models like these.
- Nyman et al. has an easily understood model which models the whole process up to death (12). In this model, all individuals who survive the first year after a cardiovascular event will end up in a "chronic state" and be there until their death.
- Weinstein's model is possibly the most extensive of those mentioned here (13). This model has five health states; persons without CHD, persons with new CHD, persons with CHD, persons who survived up to the age of 85 years, and death. Hence this

model has two different absorbing states; survive 85 and death. Individuals in the state “new CHD” will only be there the first year, and after that transfer to “CHD”, “survive until 85” or die.

1.2 STUDY OBJECTIVE

The objective of this project was to create a CVD model which can be used in economic evaluation of an array of CVD interventions (life style changes, pharmaceuticals *etc*.). The model is specifically designed to handle primary prevention strategies, such as reductions in the levels of serum cholesterol or blood pressure. In order to evaluate a specific intervention, the model requires data on effectiveness. Effectiveness data are not included in this report, as this is a description of the model and the generic input, not an economic evaluation.

2 Methods

2.1 GENERAL MODEL CONSIDERATIONS

One assumption underlying this model is that the baseline event rates are best obtained from country specific sources, while the relative change in those events (*i.e.* the intervention effectiveness) can be based on available trial results from any country.

The model is a state transition model (Markov model) in which the risk of various CVD events, as far as possible, is based on population data (age and sex specific population incidence rates). In practice, CVD interventions will be applied within population groups at increased risk. It is therefore necessary to adjust the population risks with relative risks that are specific for the specific intervention groups. These relative risks are taken from various cohort studies.

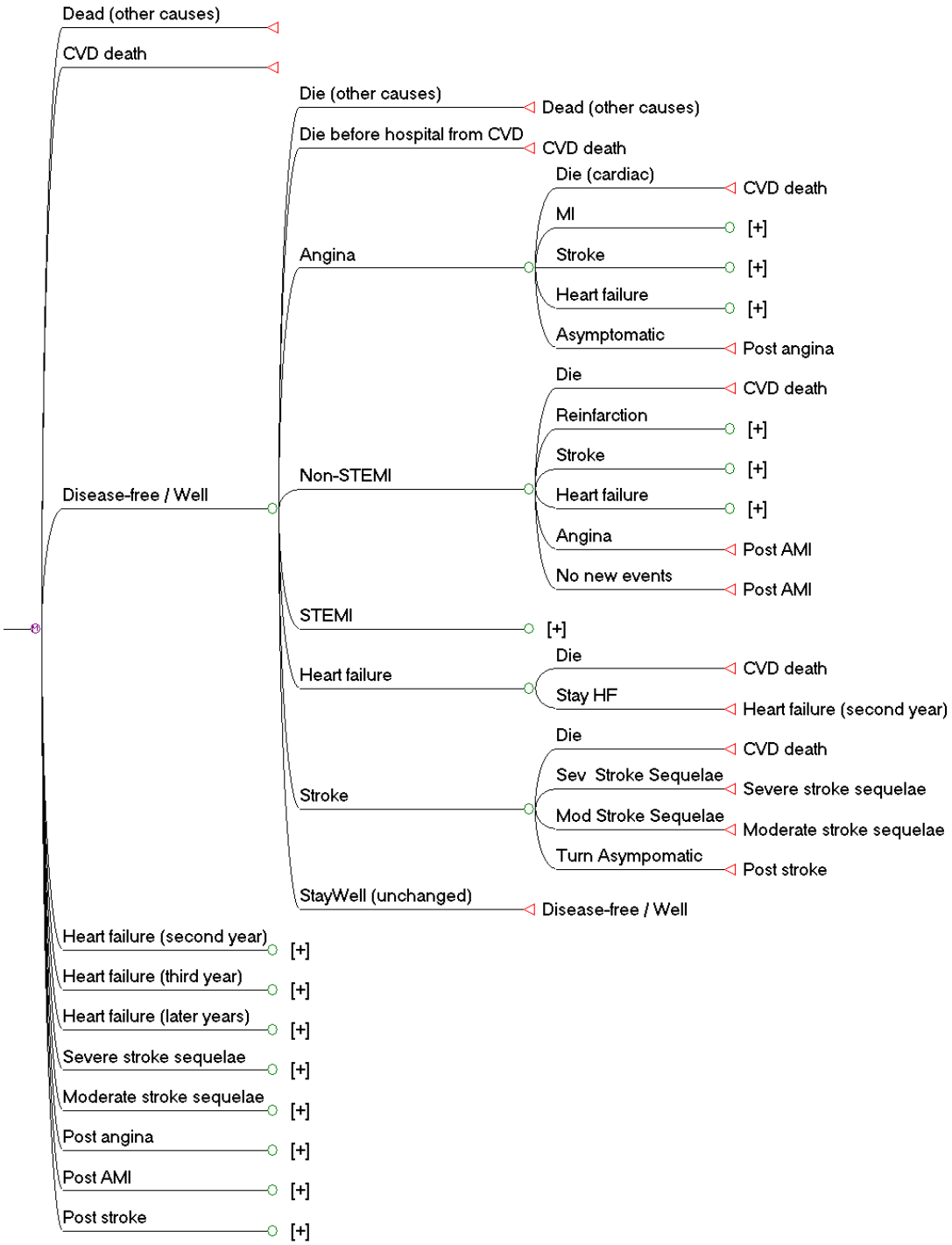
The time cycle is by default one year, but other cycle lengths are possible to implement when this is relevant for specific scenarios or interventions. The earliest possible starting point for the model is at the age of 30, due to sparse data on younger age groups. The model follows the cardiovascular disease progression for specified groups of people until most are dead at the age of 100. All relevant costs and events related to cardiovascular disease will be recorded as the disease progresses.

In the model (figure 1 and 2), a given average population is run through their (cardiovascular) life with given probabilities. The whole population is assumed to be disease-free (asymptomatic without any prior experience of CVD) at the beginning, but individuals are at risk of different primary events (see below). After each event, they are at risk of moving to different health states. The next period (year), those that have experienced a primary event, are at risk of secondary events and again moving to other health states.

CVD is in this model defined to be angina pectoris, acute myocardial infarction (AMI), stroke and heart failure.

In figure 1 and 2, [+] means that parts of the model is hidden. This is done because those arms are similar to other arms (except for probabilities of events *etc.*)

Figure 1



In Figure 1, the model structure is depicted for the first year after getting cardiovascular disease. The first column shows the different health states. The population starts in state ***disease-free/well***. Here, the primary events are:

- Angina
- AMI (STEMI and non-STEMI separate)
- Stroke
- Developing heart failure
- Die before hospital from CV
- Die from other causes

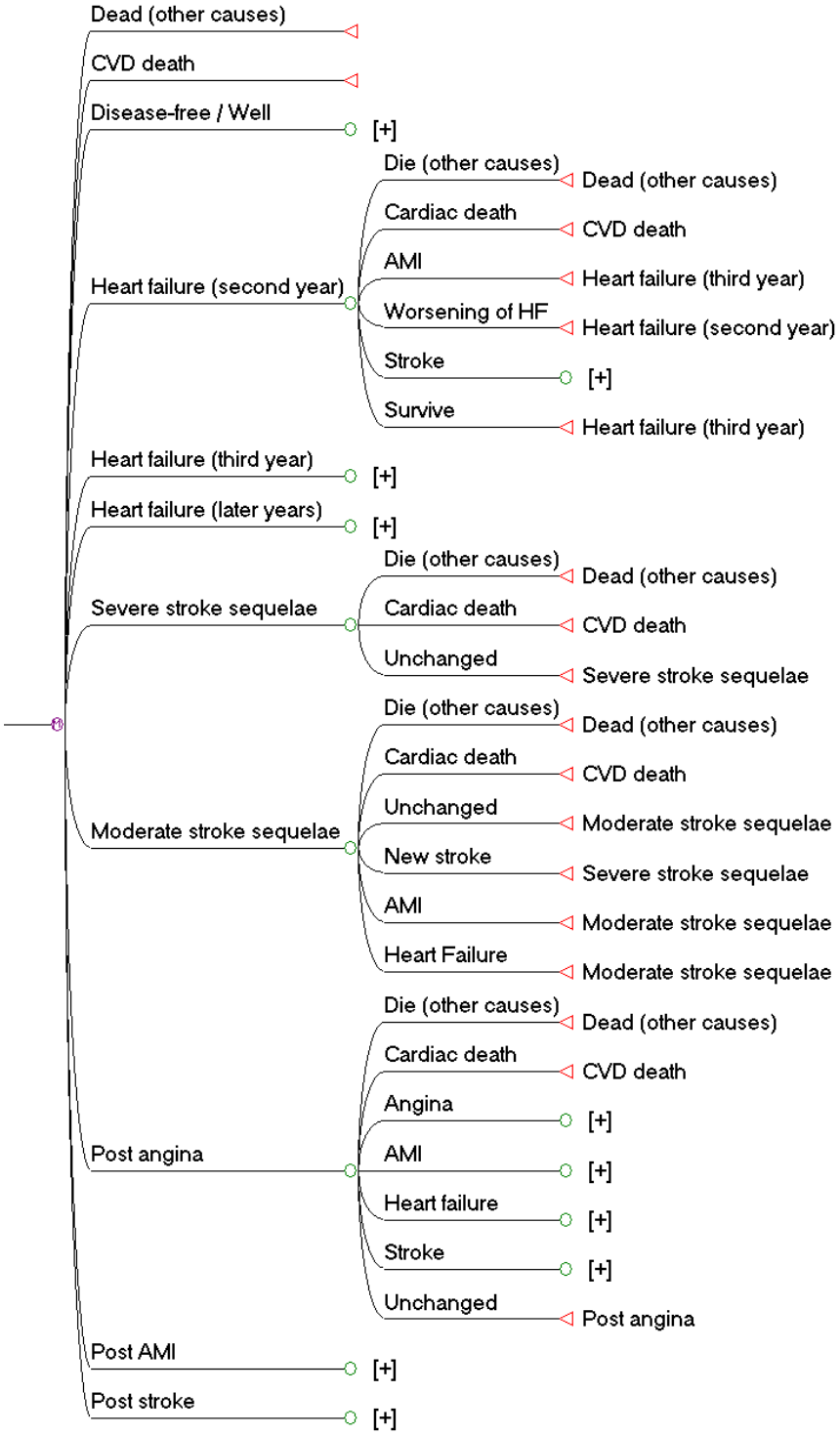
The patients may experience more than one event during the first year. These are shown by several branches to the right of each primary event. For example, a person who developed angina may die, have an MI, develop stroke, develop heart failure or turn asymptomatic. Transition probabilities after primary events are described in section 2.5.
After these primary events, there are assigned probabilities of moving into different health states. The health states included in this model are:

- Dead (dead after CVD and other causes separate)
- Disease-free
- Heart failure (divided into 3 different based on disease history)
- Moderate stroke sequelae
- Severe stroke sequelae
- Post CVD (divided into 3 different based on disease history)

Also when being in the different health states, there are risks of new events (secondary events). In addition to those mentioned under primary events, reinfarction and worsening of heart failure are secondary events (see figure 2).

In Figure 1 and 2, [+] denotes health states where the subsequent sequence of events are the same as elsewhere in the model. All health states called “post…” implies that patients in these states are asymptomatic, but compared to the disease free who have never had any CVD manifestation, their risk of subsequent CVD events is increased. In general, transitions from a permanent severe health state (*e.g.* severe stroke sequelae) to less severe states (*e.g.* heart failure) are omitted from the model because such transitions would imply cost savings that are not real (see chapter 2.7 on health benefit).

Figure 2



2.2 TRANSITION PROBABILITIES

All probabilities of the first cardiovascular event are based on Norwegian registry data (1, 14-18) (see section 2.3). With respect to the risk of secondary events, we used data published from the EuroHeart survey (19-23), or GRACE (24, 25) (see section 2.5). For probabilities not available in these registries, we used other published registries and cohort studies (26-

31), meta-analyses (32, 33) or randomised controlled trials (RCT's) (34-43). Probabilities based on RCT's (or meta-analyses of RCT's) were generally assumed to be biased down due to rigorous inclusion criteria. Hence these probabilities were adjusted upwards to be closer to real life. Lacking solid data here, we used a factor of 1.5 by assumption (varied between 1 and 2 in sensitivity analyses).

Only data on in-hospital rates ***and*** 6-month rates were available for some transition probabilities. If so, the probability of events the last 6 months of a year were assumed to be equal to the probability the first 6 months except for the in-hospital events. Hence, one-year probabilities were assumed to be approximately the double of what is observed the first 6 months, subtracted the observed rates in-hospital.

In some cases, we did only succeed in finding data based on follow-up that lasted for in-hospital-stay ***or*** 6 months. In these cases, data were adjusted to fit a one-year perspective. The choice of adjustments is shown in footnotes to each table.

2.3 PRIMARY EVENTS AND HEALTH STATES

Individuals are symptom-free with respect to CVD when they enter the model, but may have sub-clinical atherosclerosis. It is assumed that no other diseases are influenced by interventions for CVD, and only CVD are accounted for. With disease-free, we mean a health state without any symptoms or signs of prior or current cardiovascular disease. Different levels of risk factors (including diabetes), is in this relation not considered to be disease (*i.e.* CVD). The risk of disease events should ideally be based on Norwegian national data. Unfortunately, no national database is available, and we had to rely on regional Norwegian databases and a Norwegian prospective cohort study. Different *primary* events that healthy individuals can suffer and their data sources are presented in table 1.

Table 1 Sources of age-dependent risk for cardiovascular events

Cardiovascular event	Registry
Angina	HUNT (new angina without earlier CVD) (14)
Non-STEMI	HKS (16) + Riks-HIA (26)
STEMI	HKS (16) + Riks-HIA (26)
Heart failure	HKS (16)
Stroke	Innherred (17)
Cardiovascular death	HKS (first time stroke, AMI and heart failure) + SSB.no (1, 16)
Death from other causes	SSB.no (1)

All data expressed in age (in one-year groups) and sex-specific incidence rates.

Because no clinical registry data exist for the incidence of angina, we had to rely on a prospective cohort study from the county of Nord-Trøndelag (HUNT (14)). Based on data for those free of all CVD in 1985, the number of "prior or present angina" in 1996 gave 11-year

incidences of angina. These numbers were then translated to age-specific 1-year incidences. This method may bias the incidence of angina down because some people who develop angina during the 11-year period die before they are able to report it.

The incidence rates for AMI and heart failure were based on registry data from the HKS-register. Such data may overestimate the risk of first-time events if earlier events of a different type and in the same patients are not captured for technical reasons. To partly overcome this potential bias, individuals who had any prior recorded event of any cardiovascular disease in the HKS, were excluded. This potential bias, however, is not present for the incidence of angina, because data here were based on a cohort study (14) from which we only extracted data on angina in patients without previous CVD events.

The HKS-registry does not distinguish between STEMI and non-STEMI infarctions. However the Swedish Riks-HIA (26) have reported STEMI and non-STEMI, and we assumed that the Swedish data would be similar to the Norwegian. Based on this, we used incidences from HKS and divided then into two groups based on data from a Swedish registry (Riks-HIA).

Data on incidence of stroke were available from the HKS-register, but we chose to use the regional stroke register from Innherred because these data are presumed to be better validated (17). The data cover the period 1994-1996 in Innherred, a part of the county Nord-Trøndelag. In this register, all incident strokes in a two-year period were recorded and validated. The data used in the model was based on the published results, providing age- and gender-specific incidence rates in 12 different groups. Other Nordic data suggest that incidence rates have been unchanged since the 1990's (44)

We divided the health state "dead" into "dead from cardiovascular causes" and "dead from other causes". This was done in order to allow for later analyses of the causes of death. The probability of sudden death from cardiovascular disease was based on the HKS-register (16), which includes death before hospital of; AMI, stroke and heart failure. Probability of dying from other causes is based on mortality from all causes, subtracted by all deaths from cardiovascular causes (I00-I99). Death from the HKS-register was controlled against the Norwegian registry for causes of death. Such registries are known to have some limitations (see discussion), however it is likely to be the best available source on causes of death.

2.4 RISK FACTORS

When the model is used to analyse an intervention in a specific group of patients, for example a group of smokers with hypertension, the risk of CVD events need to be adjusted up or down depending on the risk factor levels, and corresponding effect estimates. The magnitude of the adjustment factors and their sources are shown in table 2.

Table 2 Relative risks used to adjust baseline risk up or down

Risk factor	Event	RR	Source
Smoking (yes/no)	Death from stroke	1.88 (1.38-2.34)***	SCORE (45)
Smoking (yes/no)	Stroke	1.88 (1.24-2.84)***	By assumption
Smoking (yes/no)	Death from CHD*	2.03 (1.43-2.87)***	SCORE (45)
Smoking (yes/no)	CHD	2.03 (1.28-3.22)***	By assumption
Cholesterol (per mmol/l)	Death from stroke	1.02 (1.010-1.030)***	SCORE (45)
Cholesterol (per mmol/l)	Stroke	1.02 (1.007-1.033)***	By assumption
Cholesterol (per mmol/l)	Death from CHD*	1.27 (1.13-1.43)***	SCORE (45)
Cholesterol (per mmol/l)	CHD	1.27 (1.09-1.48)***	By assumption
SBP** (per 20 mmHg)	Death from stroke	1.55 (1.25-1.92)***	SCORE (45)
SBP** (per 20 mmHg)	Stroke	1.55 (1.16-2.06)***	By assumption
SBP** (per 20 mmHg)	Death from CHD*	1.43 (1.20-1.70)***	SCORE (45)
SBP** (per 20 mmHg)	CHD	1.43 (1.13-1.81)***	By assumption
Type 2-diabetes (yes/no)	Stroke	5.93 (2.66-13.07)****	Meta-analysis of Håheim (46) and Njølstad (47)
Type 2-diabetes (yes/no)	CHD	1.99 (men) (1.69-2.35)**** 3.12 (women) (2.34-4.17)****	Meta-analysis (48)

* CHD = coronary heart disease = AMI + angina + heart failure

**SBP = systolic blood pressure

***Parentheses represent assumption about uncertainty used in Monte Carlo simulations

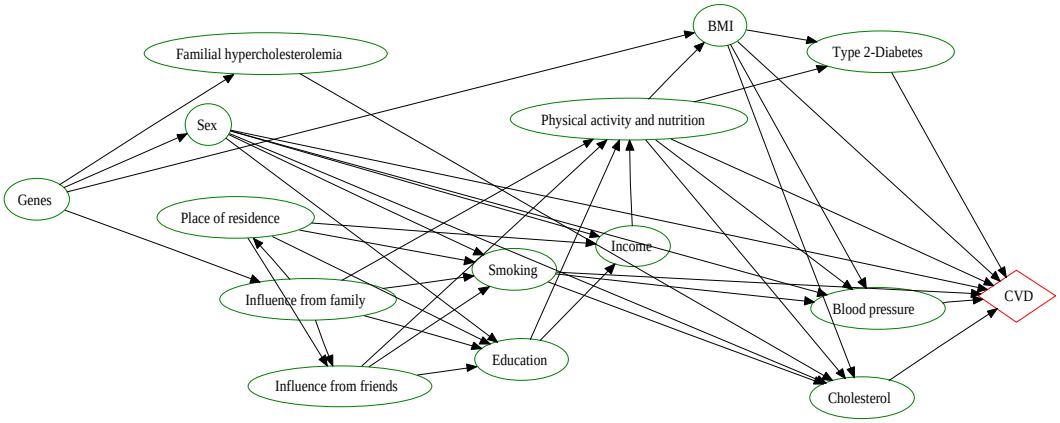
****Parentheses represent confidence intervals used in Monte Carlo simulations

We assumed that the relative effect of the risk factors; smoking, cholesterol, blood pressure and sex was the same for CVD morbidity and mortality caused by CVD. We used the SCORE equations (45) to calculate the relative effect of these factors on risk of cardiovascular death, angina, myocardial infarction, heart failure and ischemic stroke (to avoid spurious outcomes based on little data, the risks were assumed to be equal for everyone above 70 years). In SCORE, the calculations are based on measurements of cholesterol in mmol/l and systolic blood pressure (SBP) in mmHg. This is also the way it is put into our model, however, to make the table easier to relate, RR for SBP is shown per 20 mmHg. Smoking and diabetes were adjusted for as dichotomous variables. Because the relative risks from SCORE don't include confidence intervals, we made assumptions regarding parameter uncertainty to be used in the Monte Carlo simulations. The logarithm of the standard deviation was ¼ of the logarithm of the RR (approximately equal to +/- 50% variation. Since the RR's of other events than death was based on the assumption that these RR's are the same as for death, more uncertainty around these parameters seems logical, we hence set this to 1/3 of the logarithm of the RR. Reference value for all these risk factors are the average in the population (see appendix A.4).

The risk of CVD events is influenced by several factors, and there are potential interactions between these factors. How all these risk factors influence CVD and each other is not known

with certainty, but it is likely to be a non-linear relationship. The complexity of these relationships makes it unfeasible to incorporate all possible risk factors and the correlation between them, into a model. This is both due to the fact that consistent and reliable data are hard to find, and because the transparency of the model would be reduced. Figure 3 illustrates a causal web for the most common risk factors for cardiovascular disease and how one might assume that they influence each other.

Figure 3 Assumed causal web of risk factors



In line with figure 3, we made the following assumptions:

- The effect of BMI (body mass index), physical activity and diet on the risk of CVD is captured through the presence of diabetes, blood pressure and cholesterol level
- The effect of income and education is captured through sex, age, smoking state, cholesterol level, blood pressure and presence of diabetes
- The effect of family history is captured through blood pressure, cholesterol level, smoking state and diabetes
- Familial hypercholesterolemia will only influence the risk of CVD through cholesterol level

Even though this risk model captures several risk factors, it is still a simplification of the real world. One example is the observed association between smoking and education. It is unlikely that smoking affects educational attainment directly or that education affects smoking directly. It is more likely that some other underlying factors affect both, which then explain why there is a connection.

To include all adults above 30 years of age, we needed the average level of all risk factors at different ages (see appendix A.4). Averages for the rate of daily smoking, systolic blood pressure and cholesterol levels were based on the HUBRO, OPPHED and TROFINN studies (49-51). For smoking rates, a logistic model was fitted to calculate the average at ages not reported in the studies, for SBP and cholesterol, a quadratic regression model was fitted. These results are also presented in the NORRISK article (52). The proportion of each sex in each age group is based on numbers from Statistics Norway (SSB). The prevalence of diabetes was based on a Norwegian study using self-reported presence of diabetes (53).

We assumed throughout the model that average level of risk factors implies average risk.

All risk factors are assumed to be declining with age by a factor of 2.2% per year. These declines may be higher or lower depending on end point and risk factor. The 2.2% are a result calculated based on Prospective studies collaboration (54).

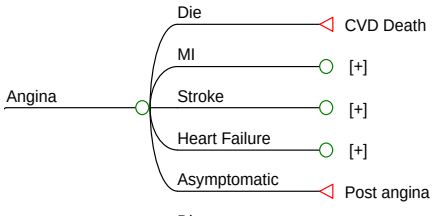
2.5 TRANSITION PROBABILITIES THE FIRST YEAR AFTER A PRIMARY EVENT

Each of the primary events described in section 2.3 and figure 1 may be complicated by subsequent events or conditions. Different health states will then describe their clinical condition, and if relevant, their disease history. In sections 2.5.1 to 2.5.4 these events and the transition probabilities of getting new events and conditions within the first year after primary events are described. Here, data were taken from foreign registries or randomised controlled trials (RCTs). To make all probabilities of death dependent on age, we used the following method. We compared the mortality risk in the registry or trial with the mortality in the CVD free population (1) of the same age as the mean age in the registry or trial. The excess mortality in the registry or trial was expressed as a relative mortality risk. We then used this relative risk to estimate age dependent mortality risks by means of the mortality risk at different ages in the healthy population (see appendix A.3). The relative mortality risk was assumed to be declining with 2.2% per year in the same way as risk factors (see section2.4).

2.5.1 Angina pectoris

Angina pectoris may lead to:

- Death
- AMI
- Stroke
- Heart failure



Angina was modelled as an event and not a chronic condition because it is assumed that the great majority of patients are relieved from their angina pain through either medication, PCI or CAB. After treatment for angina, patients will be in the health state “post angina”, unless they get a new cardiovascular event.

Table 3 Probabilities of events among patients with angina

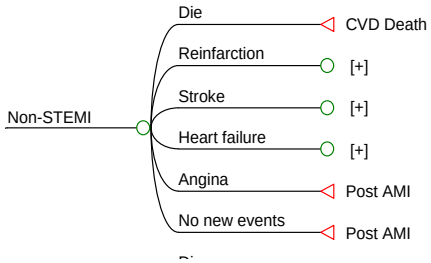
Description	Value	Low	High	Time	Comment	Age (mean)	RR
Cardiovascular death (men)	0.0108	0.0060	0.0156	First year	Based on Daly et.al. (EuroHeart) (19)	60	3.7
Cardiovascular death (women)	0.0134	0.0071	0.0197	First year	Based on Daly et.al. (EuroHeart) (19)	62	11.6
AMI (men)	0.0153	0.0096	0.0211	First year	Based on Daly et.al. (EuroHeart) (19)		
AMI (women)	0.0173	0.0101	0.0245	First year	Based on Daly et.al. (EuroHeart) (19)		
Stroke (men)	0.0119	0.0069	0.0170	First year	Based on Daly et.al. (EuroHeart) (19)		
Stroke (women)	0.0110	0.0053	0.0168	First year	Based on Daly et.al. (EuroHeart) (19)		
Heart failure (men)	0.0153	0.0096	0.0211	First year	Based on Daly et.al. (EuroHeart) (19)		
Heart failure (women)	0.0181	0.0108	0.0254	First year	Based on Daly et.al. (EuroHeart) (19)		

In the EuroHeart Survey, information on the one-year probabilities of cardiovascular death, nonfatal AMI, cerebrovascular accident (stroke) and heart failure after angina were captured (19). Because the EuroHeart Survey is a high quality survey with much data from several European countries (including Sweden, Denmark and Finland), we reckoned this would be the best possible input data on what happens after angina in Norway. For cardiovascular death, probabilities were added into the model as relative risks. These were calculated from the probabilities in table 3 compared with average risk of cardiovascular death in the Norwegian population for the age group closest to the average in Daly et.al.

2.5.2 AMI (non-STEMI and STEMI)

AMI may lead to:

- Death
- Reinfarction
- Stroke
- Heart failure
- Angina



The model makes a distinction between ST-elevation acute myocardial infarctions (STEMI's) and non-ST-elevation acute myocardial infarctions (non-STEMI's) when AMI is a primary event (Table 4). This is because probabilities of subsequent events differ between non-STEMI and STEMI. The reason for not distinguishing between STEMI and non-STEMI when AMI is a secondary event (*e.g.* reinfarction), is lack of data. One-year mortality after STEMI and non-STEMI seems to be close to equal (26), hence mortality after AMI as a whole is taken from a Swedish registry (26).

AMI was modelled as an event. This means that during each year the model runs, there is a probability of getting AMI. After treatment, patients are in the health states post AMI, unless they get a new cardiovascular event.

Reinfarction is in this model defined as having a new myocardial infarction during the first 6 months after an AMI. Later AMI's are defined as a new infarction, and hence a secondary event (see section 2.6.1). The probabilities of death after reinfarction was based on the DANAMI-2 trial (36), which is a large Danish RCT. All other events after reinfarction were based on the assumption that the probabilities of events are equal after the first and subsequent infarctions. This might be an ***under***estimate if the time perspective was the same. In the model, however, events after reinfarction come in a shorter period of time than after the first infarction (which might be an ***over***estimate), and hence we assume that this levels out.

The probabilities related to AMI are in table 4.

Table 4 Probabilities of new events after AMI (non-STEMI and STEMI)

Description	Value	Low	High	Time	Reference
Dying after AMI	Varies by age (see appendix A.5)			One year	Swedish official data (26)
Reinfarction after non-STEMI	0.014	0.011	0.017	In-hospital**	Hasdai, EuroHeart 1 (20)
Reinfarction after STEMI	0.027	0.022	0.032	In-hospital**	Hasdai, EuroHeart 1 (20)
	0.018	0.015	0.020	6 months***	
Stroke after non-STEMI	0.009	0.007	0.011	In-hospital***	Budaj, GRACE (25)
	0.021	0.018	0.023	6 months***	
Stroke after STEMI	0.013	0.011	0.015	In-hospital***	Budaj, GRACE (25)
Heart failure after non-STEMI	0.246	0.235	0.256	In-hospital	Fox, GRACE (24)
Heart failure after STEMI	0.288	0.277	0.298	In-hospital	Fox, GRACE (24)
Angina after Non-STEMI*	0.090	0.074	0.106	One year	Based on ICTUS (34)
Angina after STEMI*	0. 114	0.083	0.145	One year	Based on Zijlstra 1999 (35)
Dying after reinfarction*	0.242	0.135	0.369	30 days	Based on Andersen, DANAMI-2 (36)
Stroke after reinfarction	Assumed to be the same as after first AMI				
Heart failure after reinfarction	Assumed to be the same as after first AMI				
Angina after reinfarction*	Assumed to be the same as after first AMI				

*These are in the model adjusted due to being RCT-data (see section 2.2)

** In-hospital probabilities are assumed to be half of one-year-probabilities (1/3 – 1 in sensitivity analyses)

***Here exist both in-hospital and 6 month data (see formula under 2.2)

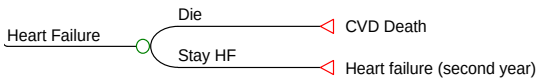
The probability of angina after non-STEMI was based on the ICTUS study (34), where re-hospitalisation for anginal symptoms after non-STEMI was reported. The probability of angina after STEMI was based on Zijlstra et.al. (35). This was a Dutch randomised controlled trial (RCT) with 5-years follow-up-data on 395 patients with acute myocardial infarction. Angina in this trial is assumed to be those readmissions for ischemia that were not reinfarctions: 101+180-56=225. We assumed that the probability of angina after STEMI is constant over time, and hence divided the observed numbers by 5 (225/5=45). The probability (11.4%), was similar to that observed in another trial, the PAMI-I TRIAL (55).

All other probabilities after AMI was based on the Euro Heart survey (19-23) or GRACE (24, 25), which are well recognised international registries.

2.5.3 Primary heart failure

Heart failure may lead to:

- Death
- (AMI)
- (Stroke)
- (Angina)



Even though heart failure may lead to AMI, stroke and angina, these events are omitted during the first year after development of heart failure (Table 5). The reason is that it is difficult to find probabilities of these events.

We distinguish in our model between heart failure that occurs directly without prior symptoms or disease (primary heart failure), and heart failure that occurs within the period shortly after AMI or angina (secondary heart failure). We assume that secondary heart failure in some cases can be more or less cured, and that those patients go to health states post AMI or post angina in stead of heart failure.

Table 5 Probability of new event after heart failure

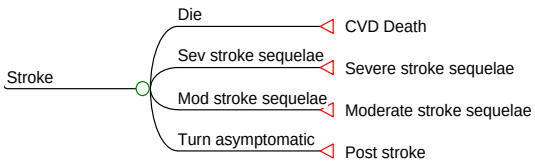
Description	Value	Low	High	Time	Comment
Continued heart failure	0.500	0.333	0.750	6-12 months	Expert opinion (SH)
Dying from secondary heart failure	0.290	0.240	0.340	1 yr	Based on EuroHeart 2 (21)
Dying from primary heart failure (men)	0.173	0.132	0.213	1 yr	Based on EuroHeart 2 (22)
Dying from primary heart failure (women)	0.163	0.116	0.209	1 yr	Based on EuroHeart 2 (22)

The probability of dying after primary heart failure was based on data from a EuroHeart publication by Rosolova et.al. (22). Heart failure after MI or angina (here: secondary heart failure) is usually a more serious condition than when getting heart failure without prior disease (primary heart failure). Hence a EuroHeart-II-presentation by F.Follath at the 2005 congress of the European Society of Cardiology (ESC) was used (21), since they included more serious cases of heart failure than Rosolova et.al.

2.5.4 Stroke

Stroke may lead to:

- Death
- Severe stroke sequelae
- Moderate stroke sequelae
- (AMI)



Even though stroke also may lead to AMI, the probability of getting AMI the same year as (but after) getting stroke, was omitted due to lack of data (Table 6). AMI can be seen as less severe than stroke or death, and the omission will hence lead to only small loss of substantial information.

The probabilities of developing sequelae after stroke were based on Riks-Stroke, a Swedish registry (29). It was assumed that half of those who live at home (14.4% / 2) and received assistance were having moderate sequelae. The other half was then assumed to have severe sequelae. In addition all who live in institutions are assumed to have severe stroke sequelae (8.5% + 1.2%). Riks-Stroke has only published 3 month and 2 year data on mortality, and we have hence not included Riks-Stroke data for mortality. A weighted average of data from a Swedish and a Danish registry formed the basis of the probability of death the first year after stroke (27, 28).

Table 6 Probabilities related to stroke

Description	Value	Low	High	Comment
Dying the first year after stroke	0.338	0.315	0.361	Based on two studies: Terent et.al. (27) and Kammersgaard et.al. (28)
Moderate sequelae the first year after stroke	0.072	0.060	0.084	Based on registry data, Riks-Stroke (29)
Severe sequelae the first year after a stroke	0.169	0.158	0.180	Based on registry data, Riks-Stroke (29)

2.6 HEALTH STATES (MORE THAN ONE YEAR AFTER FIRST EVENT)

Those who have not yet experienced a CVD event will be in the health state "disease-free". After a CVD event, the patient will be in one of the following health states which are mutually exclusive (each health state lasts one or more years):

- Dead
- Heart failure
- Severe stroke sequelae
- Moderate stroke sequelae
- Post CVD (asymptomatic)

The health state "post CVD" encompasses patients who have had a CVD event, but are (almost) asymptomatic and are not in any of the other health states listed above. These patients are not necessarily all 100% asymptomatic, but might have some mild symptoms, but they do not have stroke sequelae or heart failure.

When patients are in any of the health states stroke sequelae, heart failure or post CVD, they are at risk of new CVD events as specified in sections 2.6.1-2.6.3. These risks are modelled as one-year-probabilities. After each year, persons in each health state (also the dead) are counted, and in the end these are summarised to give total remaining life expectancy for the cohort.

2.6.1 Secondary events after cardiovascular disease

Because Markov models have no memory, we decided to separate the health state "Post CVD" based on what kind of CVD the patients had been treated for (angina pectoris, AMI, stroke). This allows the presentation of the distribution "post CVD" states.

All probabilities of new events when in "Post CVD" were translated into relative risks as there are limited data on the variations in these transition probabilities by age. This was done by comparing the probabilities with the underlying incidence rates in the population (1). The relative risk estimates of new events more than one year after CVD for those in any of the post-CVD states are presented in Table 7, 8 and 9. The probabilities are adjusted according to the same risk factors as for primary events.

Table 7 Relative risks of events more than one year after AMI compared to healthy subjects

Description	Value	Low	High	Comment
AMI*	3.05	1.47	4,60	DANAMI-2 (37)
Angina*	21.7	15.8	27.6	Zijlstra (35)
Death*	Varying by age (see app. A.5)			OPTIMAAL (38), DANAMI-2 (37), and RIKS-HIA (26)
Stroke*	2.77	2.08	3.47	OPTIMAAL (38)

*These are in the model adjusted due to being RCT-data

The relative risks in table 7 are for those who are in the health state Post AMI as illustrated in figure 2. The probabilities of AMI, angina and stroke were based on three different trials with long follow-up (35, 37, 38). The probability of death after AMI was based on two RCT's which both had about 3 years mean follow-up. A weighted average gave 14.07% 3-year mortality. The mean age was 66 years in the two trials. The probability of death after the first year is, based on appendix A.5, assumed to be 14% - 9% = 5% for each two-year period in the age group 60-69 years old. In other age groups, the death rates are assumed to increase with the same relative difference as the one-year mortality. More on these is in appendix A.5.

Table 8 Relative risks of events more than one year after angina compared healthy subjects

Description	Value	Low	High	Comment
AMI (men)	3.88	2.24	5.60	Assumed to be half of the probability first year, SMM-report nr
AMI (women)	1.17	0.76	1.59	5/2002 (56)
Angina*	11.32	8.30	14.29	NOKC-report nr 8/2004 (57)
Death	1.23	0.82	1.65	Based on meta-analyses from Nordmann (32)+ HKS (16)
Stroke (men)	5,34			
Stroke (women)	5,26			Risks based on relationship between angina and well first year after angina (2.3 and 2.5.1) Daly et.al. (19)

*These are in the model adjusted due to being RCT-data

The relative risks in table 8 are for those who are in the health state Post angina as shown in figure 2. The relative risk of death after angina was based on data from Nordmann et.al. (32). The risk was based on the probability of death among both intervention and control arms, divided by the Norwegian population average for 62-year-olds, which are described in section 2.3 (62 is the mean age in the studies from Nordmann et.al.). Probabilities of heart failure more than one year after AMI, angina and stroke were assumed to be zero due to lack of data. The probabilities of AMI and angina were based on the economic evaluation from NOKC mentioned above (58).

The relative risk of stroke after angina was based on the relationship between the risk of stroke when well, compared to the first year after onset of angina. Because the average age in Daly et.al. (19) was 62 years old, we based the RR calculations on stroke incidence for 62-year-olds (chapter 2.3). Hence the relative risks were 0.0119/0.00223=5.34 for men and

0.0110/0.00209=5.26 for women. These relative risks are a bit higher than after AMI and stroke. We have elaborated more on this in the discussion.

Table 9 Relative risk (RR) of events more than one year after stroke without sequelae compared to well

Description	Value	Low	High	Comment
AMI	3.51	1.78	5.33	van Wijk (39)
Death	4.91	3.86	5.97	van Wijk (39) and SSB (1)
Stroke	2.82	1.81	3.48	van Wijk (39)

These relative risks (table 9) are for those that are in the health state post stroke as shown in figure 2. All probabilities of events for those who have no sequelae after stroke are assumed to be similar to the probabilities for the group of people that get transient ischemic attack (TIA). The probability of AMI, death and stroke is based on the Dutch TIA Trial of 2,473 patients with TIA or minor ischemic stroke (39). This was a cohort study with a mean follow-up of 10 years. The figures for deaths and stroke are given in the paper, while AMI is estimated by subtracting stroke, cardiovascular and cerebrovascular deaths from "major vascular event". The relative risk of dying compared to healthy subjects is based on the probability of death in van Wijk, divided by the Norwegian population average for 65 years olds (which is the mean age in van Wijk et.al.). The data on deaths were adjusted down with 28%, because 28% of the deaths were non-cardiovascular, and our model includes these death rates separately. The risk of angina and heart failure after TIA is not estimated due to lack of data, and therefore not included in the model.

2.6.2 Secondary events when having heart failure

Heart failure is one of the conditions that are well reported in the Euro Heart survey. Hence the majority of the probabilities of events more than one year after onset of heart failure are from EuroHeart.

Table 10 Relative risks (RR's) of events when having heart failure (HF)

Description	Value	Low	High	Comment
Dying 2nd year after HF (women)	6.67	6.16	11.04	Rosolova, Euroheart 2 (22)
Dying 3rd year after HF (women)	7.61	5.08	10.15	Rosolova, Euroheart 2 (22)
Dying later years after HF (women)	2.45	0.90	4.00	Rosolova, Euroheart 2 (22) and SSB
Dying 2nd year after HF (men)	5.05	3.24	6.86	Rosolova, Euroheart 2 (22)
Dying 3rd year after HF (men)	4.62	2.90	6.33	Rosolova, Euroheart 2 (22)
Dying later years after HF (men)	2.13	0.96	3.31	Rosolova, Euroheart 2 (22) and SSB
Stroke*	6.80	3.40	13.61	Based on SAVE (40) and SOLVD (41)
Worsening of HF	9.58	9.04	10.13	Cleland, Euroheart (23)
AMI after HF (men)	1.5	0.6	3.8	Based on Mosterd et.al. (30)
AMI after HF (women)	4.1	1.8	9.3	Based on Mosterd et.al. (30)

*Adjusted due to being RCT-data

Data on yearly incidence of stroke after heart failure was not recorded in any of the registries we explored, and we were left with using data from RCT's. In the SAVE trial the incidence was 1.5% per year, and we adopted this for our analysis (40). In SOLVD, the incidence was

approximately the same, with slightly higher incidence for women (41). Data on worsening and dying from heart failure was based on two different publications from the EuroHeart survey (21, 23). The EuroHeart data on dying were adjusted down with 8%, because 8% of the deaths were non-cardiovascular, and our model deals with non-cardiovascular death rates separately. Death rates the fifth year and all following years after onset of heart failure are assumed to be the same as for the fourth year. All relative risks in table 10 are reduced by a factor of 2.2%. Such reduction is based on the fact that the impact of risk factors (*e.g.* blood pressure, cholesterol level) declines by age. For example, the relative risk of stroke declines by 2.2% per year of age. Such declines may be higher or lower depending on end point and risk factor. The data on worsening of heart failure from EuroHeart (23) was based on readmissions within the first 12 weeks after discharge; (591+460)/8463=0.124. The increased risk of AMI for patients with heart failure, compared to others, was based on Dutch registry data on non-fatal cardiac outcomes.

2.6.3 Secondary events when having stroke sequelae

As mentioned in 2.5.4, sequelae after stroke is divided in two based on severity. Being institutionalised with stroke sequelae is reckoned as a severe health state. Hence we have not included any new CVD when being in the health state "severe stroke sequelae".

Table 11 Relative risks (RR) of events when having stroke sequelae

Description	Value	Low	High	Comment
AMI when having moderate stroke sequelae	4.41	3.32	5.28	Based on meta-regression from Touzé et.al. (33)
RR of heart failure when having moderate stroke sequelae compared to well	2	1	4	Expert opinion (ISK)
Moderate stroke sequelae becoming severe	4.30	3.92	4.62	Meta-analysis of Hillen (42) and Caro (43)
RR of dying with moderate stroke sequelae compared to no sequelae	2	1.5	2.5	Based on Peeters (31)
RR of dying with severe stroke sequelae compared to no sequelae	3	2.25	3.75	Based on Peeters (31)

The probability of AMI was based on a meta-regression of 29 studies published until March 2005 (33). The risk of dying with stroke sequelae was based on a study by Peeters et.al. (31). This article report life expectancies for healthy and survivors of stroke from the Framingham Heart study. Based on these life expectancies, this relative risk was assumed to be 3 for severe sequelae and 2 for moderate sequelae. Because this death rate is based on all-cause mortality, the probability of dying from other causes will be 0 in this case. When having moderate stroke sequelae, there is a chance of having a new stroke. All who get a new stroke when having sequelae are assumed to get severe stroke sequelae. The risk of this transition was based on a combination of the probabilities of getting a new stroke is the trials of Hillen (42) and Caro (43).

2.7 MEASURES OF HEALTH BENEFIT

The mortality risks of the model are translated into life expectancy. By employing interventions in one arm of the model, benefits of these interventions can be expressed in terms of life year gains (*i.e.* in differences in life expectancy between the two arms). Interventions that reduce the risk of cardiovascular events also entail improvements in quality of life. The model is prepared for quality adjustment of life-years. The decision analyst then need to assign quality of life weights to all different health states and the model will then estimate QALY gains.

2.8 INTERVENTION EFFICACY

The model can in principle capture the benefits of any cardiovascular intervention. The model is structured such that efficacy of interventions need to be expressed in terms of relative risk reductions. By using data on the specific patient group that is relevant for the interventions, baseline risk can be computed and consequently the benefits in absolute terms (life years gained or quality adjusted life years gained). Efficacy data are gathered as a separate process, typically on the basis of a systematic review and meta-analysis. Intention-to-treat (ITT)-analyses is used whenever possible. This principle implies that the estimated effects stems from treatment of less than 100% of the patients in the trials due to non-adherence/non-compliance.

2.9 COSTS

The medication costs are specific for each intervention and are not explored here. Because the data on effectiveness will be based on RCT's that are analysed according to the intention-to-treat principle, the intervention costs will be adjusted downwards according to non-compliance as observed in the trials.

The costs of all cardiovascular events and subsequent health states are listed in Table 13. The costing is based on identification of costs, quantification of costs (utilisation of care) and unit costs (see appendix A.8). Ideally, utilisation of health care should be based on register data from routine care. Unfortunately, such data are not available for Norway, and we had to employ expert judgement except for treatment of stroke where a recent study provided data (59). Unit costs were based on fee schedule for Norwegian doctors (60), fee schedule for outpatient clinics (61), the DRG price list (62) and Physicians' desk reference (63). All costs were expressed in 2005 Norwegian Kroner (NOK).

Table 13 Cost parameters (all costs in 2005 Norwegian Kroner (NOK))

Description	Value (NOK)
Cost of developing angina and have treatment	77 494
Cost of being in the state post MI for a year	2 980
Cost of being in the state post stroke for a year	2 163
Cost of being in the state post angina for a year	2 163
Cost of dying a cardiac death in hospital	43 425
Short term costs of developing heart failure	31 756
Cost of worsening of heart failure	31 071
Cost of one year with heart failure	30 774
Cost of living in the health state moderate stroke sequelae	49 200
Costs of treating a non-ST-elevated myocardial infarction	114 932
Costs treating an ST-elevated MI	114 932
Cost of being in the health state severe stroke sequelae (*i.e.* one year in nursing home)	500 000
Cost of reinfarction	34 659
Costs incurring the first year after getting stroke	164 000
Cost of one unit DRG	30 325
Cost of GP visits when receiving statin treatment (first year)	1 071
Cost of GP visits when receiving statin treatment (later years)	536
Cost of GP visits when receiving thiazide treatment (first year)	1 101
Cost of GP visits when receiving thiazide treatment (later years)	527

For each of the interventions for STEMI and non-STEMI, we assumed that all patients below the age of 70 years have coronary angiography. We also assumed that no patients above 85 years have angiography. For the age groups between 70 and 85, we assumed evenly declining rates from 100% to 0%. For instance, this means that two thirds of the 75 year olds, and one third of the 80 year olds, get angiography.

A thorough presentation of assumed units and unit costs are presented in appendix A.8.

2.10 DISCOUNT RATE

The Norwegian ministry of Finance has suggested a 4% discount rate and this rate is used for both costs and effects in the base case analyses. However other rates can easily be explored in sensitivity analyses.

2.11 SENSITIVITY ANALYSES

The NorCaD model was developed in the computer programme TreeAge Pro 2007. This allows the use of one-way and multi-way sensitivity analyses. It also allows probabilistic sensitivity analysis using Monte Carlo simulation.

In a Monte Carlo simulation, each uncertain parameter is assigned a probability distribution. Then a single value is drawn from each distribution in every iteration and the model is run to calculate costs and effects in both arms. This procedure is repeated a large number of times, for example 10.000 times. The incremental costs and effects of such simulations are then depicted in the cost-effectiveness plane to give indications of the total uncertainty in the model. Other possible outputs of these analyses are among others, the cost-effectiveness acceptability curve (64), net benefits, value of information analysis (65) and the cost-effectiveness frontier (64).

We used the expected value of each parameter based on assumptions about their distributions to calculate the incremental cost-effectiveness ratio (ICER). This method is advocated as recommended instead of using only the single values presented in the tables. More on this can be found in Briggs et.al.(66).

The choice of distributions used in this model is, to some extent, based on the logic used in an article by Briggs et.al. (67) and later also in a book by Briggs, Claxton and Sculpher (66). For probabilities we used beta-distributions because they are restricted to values between 0 and 1. For the probabilities that arose from single trials which reported exact number of participants and events, we used a beta distribution with n and r, where n is total number of participants and r is those that experience an event. For most other probabilities, we used confidence intervals (*e.g.* from meta-analyses) to calculate suitable estimate of values for the beta-distribution parameters.

Incidences, population distribution of risk factors, age-dependent mortality risks and age-dependent relative risks were all incorporated into the model as tables. Because these parameters encompassed more than 2000 different values in total, it would not be feasible to use an individual distribution on each of these values, even though this had been optimal (if they were made dependent on each other). Instead, we used one single Normal distribution for all values in the same table.

As adherence rates and QALY values also are defined to be values between 0 and 1, we used beta-distributions for these as well. Adherence rates were incorporated as Beta(n,r) as described above. While the ranges for the QALY-values (see table 12) were assumed to be covering a 95% range of possible values and incorporated as Beta(α,β).

Costs and quantifications of cost items are assumed to follow gamma distributions, based on the probable skewness in the data. The gamma distribution is a distribution with only positive values and has a thicker left than right tale (skewed distribution). These properties are also reasonable to assume for most cost parameters (66).

3 Validation and results

As this report is a technical description of the NorCaD model, we do not provide data on any specific CVD intervention and there is no chapter with results. However, this model has gone through a validation process. All models are only just that: models. Hence, they will not always produce exactly the numbers expected and may not capture all medical details or practice variation.

The NorCaD model produced expected remaining life times that were somewhat smaller than those reported by Statistics Norway. Mainly NorCaD had problems with ages above 90 years old, because it has no data beyond age 100 years. To partly overcome this discrepancy, all probabilities of death were adjusted downwards to give the close to the same expected remaining lifetime at the ages 30, 40, 50, 60, 70, 80 and 90 years of age as that reported by statistics Norway (1). The expected remaining lifetimes from the model are in table 14.

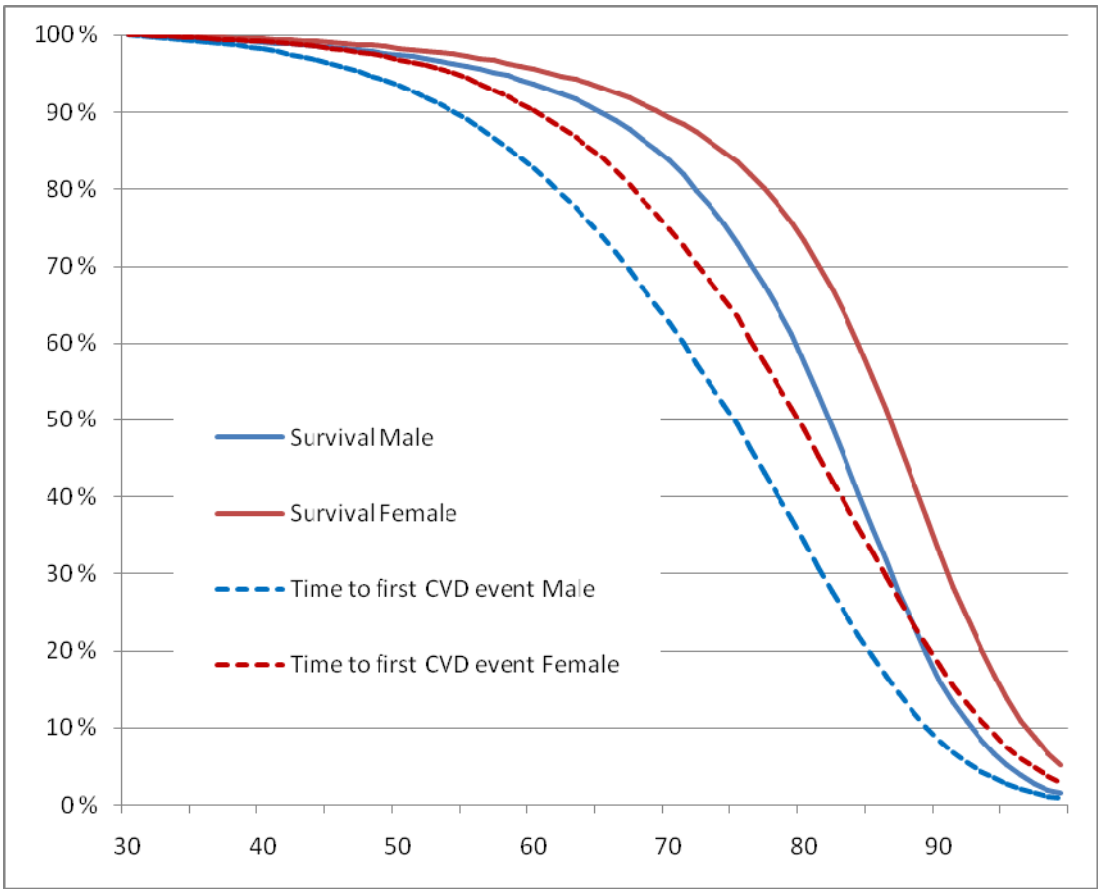
Table 14 Expected remaining lifetime for healthy subjects in the NorCaD model and from Statistics Norway

	NorCaD		Statistics Norway	
Age	Women	Men	Women	Men
30	53.16	48.80	53.16	48.80
40	43.43	39.26	43.43	39.26
50	33.93	29.95	33.93	29.93
60	24.90	21.18	24.90	21.18
70	16.54	13.43	16.54	13.42
80	9.35	7.31	9.33	7.31
90	4.31	3.56	4.31	3.57

We performed a cohort analysis of 30-year olds without prior cardiovascular disease to show how survival and time to first CVD event (or death) develops over time. This is presented in figure 4. From the cohort analysis we also summarized the costs related to cardiovascular disease. We found that expected average lifetime costs related to cardiovascular disease was NOK 550,000 for men and NOK 590,000 for women (undiscounted). The difference be-

tween men and women is due to differences in life expectancy (expected 53.2 and 48.8 remaining life years for women and men, respectively).

Figure 4 Survival and time to first CVD event (or death) for a cohort of 30-year-olds



4 Discussion

The model described in this document in principle allows economic evaluation of any type of CVD intervention, although the model was developed to evaluate primary prevention. The model is comprehensive in terms of potential events and health states, but it s still a simplification of real life both in terms of medical events and use of resources. Medical as well as resource use data stems mainly from Norway, and the results are to some extent country specific. Such a comprehensive model has considerable potential. First of all, it can be used for different health economic evaluations within the Norwegian Knowledge Centre for the Health Services. As the centre both conducts separate economic evaluations and also economic evaluations alongside systematic reviews in HTA-report, there will likely be projects on cardiovascular disease where this model can be used. Secondly, the model has a potential for use in reimbursement decisions. When pharmaceutical agencies apply for reimbursement, they have to prove both efficacy and cost-effectiveness. If they all, companies and health authorities as well, could use the same model, developed by researchers outside the industry, the comparison between different new interventions would be much easier. In addition, this could reduce the workload both in the pharmaceutical industry and government. Finally, the model could also be used in settings outside Norway with possibly some adjustments. Other HTA agencies that conduct thorough HTA reports including economic evaluations would from time to time be in need of a cardiovascular model.

While several previously published models have estimated the risk of CVD events on the basis of risk equations (typically the Framingham risk equations), we used observed incidence rates in the population and adjusted these rates up or down depending on the presence or absence of risk factors. The advantage of this approach is first that we avoid bias introduced by uncertainties in risk equations, and second that we avoid uncertainties introduced by distance in time or distance in geography. Our approach, however, is not without problems. One important issue in this context is that we use register data for incidence rates, and there may be limitations in the quality of these registers. There might however be a problem with this kind of strategy because the data stems from many different sources. This might lead to inconsistencies that are difficult to disentangle.

4.1 MODELLING INCIDENCES OF DIFFERENT CARDIOVASCULAR DIAGNOSES

There are problems in getting valid national incidence rates in Norway because we do not have a national register for cardiovascular disease. We here describe some of the problems and our choices of incidence rates.

4.1.1 Stroke incidence

Data on incidence of stroke were available from the HKS-register, but we chose to use Norwegian survey data from Innherred because data here presumably are better validated (68). This survey was conducted during the period 1994-1996 in Innherred, which is a part of the county Nord-Trøndelag. In this register, all incident strokes during a two-year period were recorded. The data we used in the model was based on the publication, which gave us age- and gender-specific incidence rates in 12 different groups.

There has been a steady decline in stroke mortality in Norway since the 1960'ies. Because standardized registrations of stroke incidence over time are lacking in Norway we do not know how much of the decrease in stroke mortality that can be explained by a decline in stroke incidence and how much by decline in case fatality (44). The incidence rates are similar to rates reported in Sweden and Denmark. Trend studies of incidence from other Nordic countries show divergent results, some demonstrated an increase and others a decrease the last 10-20 years but case fatality rate has declined. A comparison between data from the HKS-register and Innherred shows similar rates, but somewhat lower from HKS. This may be due to regional variations or time trends in incidence or due to different methods of registrations and validation. Some of the discrepancies may stem from different definition of age groups. Due to lack of standardized registrations of stroke incidence we cannot determine with certainty the reason for the discrepancy. Innherred is located in the county of Nord-Trøndelag. Data from Norhealth 2008 (69) shows that the mortality from cardiovascular diseases in Nord-Trøndelag was close to national rates in 2006. Prevalence of daily smoking was slightly lower than the average for Norway and percent with low education similar. Data from NorPD (Norwegian prescription database) show similar prevalence of statin prescribing in Nord-Trøndelag as the whole country. These are indications that Nord-Trøndelag is representative of the country. Furthermore, cardiovascular risk factors from the 1990-ies were close to the average for Norway (70). We are awaiting updated risk factor profiles from the HUNT 4 study (14), but so far Nord-Trøndelag seems to be fairly representative for cardiovascular risk profiles in Norway.

4.1.2 Incidence of acute myocardial infarction

The incidence rates for AMI and heart failure were based on registry data from the HKS-register.

The incidence rates from HKS stems from the period 2000-2001 before the introduction of new diagnostic criteria. There has been a marked increase in the registered number of acute myocardial infarctions following introduction of new diagnostic guidelines (71). Data from the HKS register showed that hospital admission rates with first time acute myocardial infarction declined during the period 1992 - 2000 while the rates were higher in 2001 (72). On the other hand, there was good agreement between incidence rates of acute myocardial infarction from the HKS 2000-2001 and the regional infarction register in Trondheim (Helse Midt-Norge) 2001-2004 for age groups below 80 years (data not shown). We consider the incidence rates from HKS to be reasonable for our modelling purposes. When HKS data are updated for the period after 2001, the AMI incidence rates will probably be substantially higher due to changed diagnostic criteria. More people that previously got the diagnosis "unstable angina pectoris" will with the new diagnostic criteria get the diagnosis acute myocardial infarction {Hagen 2003}. The rates will be higher, but the cases might have less severe disease than previously. The consequences of this diagnostic shift may mean an increase in the immediate costs because infarction patients are likely to receive more "aggressive" treatment than angina patients. In fact, the expert judgment imply that the acute costs of a non-STEMI are NOK 37,000 higher the angina ones (Table 13). We performed additional analyses where we "moved" 33% of the patients from angina to non-STEMI in the model. The results showed only minor influences on the costs (< 1.5%) and effects (<0.1%).

4.1.3 Angina pectoris

The problems getting valid data are even higher for angina pectoris. First, definitions may vary. Variation in hospital admissions may be due to elective invasive treatment. A report from OECD concluded that it was impossible to get comparable data on angina from different countries (73). Second, we have no register reporting incidences of angina. We have therefore based our estimates on self report from the HUNT study. The questionnaire has not been validated with respect to angina, but cohort studies show that people reporting angina at screening have a higher risk of death from cardiovascular diseases than people reporting no CVD. A mortality follow-up from 1989 to 2004 of people aged 65-57 years participating in a similar study as HUNT, showed that men reporting angina had a relative risk of 3 of dying from ischemic heart disease compared to healthy and MI patients had a relative risk of 4 (personal communication: Randi Selmer). Corresponding relative risks in women were 4.5 and 8. Thus, as expected people reporting angina had a cardiovascular risk between healthy and people with previous MI, pointing to validity of the self reported angina.

4.1.4 Heart Failure

The problems of getting valid data are also high for heart failure. Most registries and many RCT's do not report heart failure. In addition, the definition of heart failure varies greatly between studies. Thus, some of the variation in incidence of heart failure in this report might be due to varying definitions.

Heart failure may occur as a complication after coronary artery disease (myocardial infarction, angina pectoris), or be due to longstanding hypertension, diabetes, arrhythmias *etc*. In our model, we included heart failure both as an event (complication) after myocardial infarction or angina pectoris, and also as a condition that occurs without prior coronary event.

4.1.5 General comments on estimation of incidences

Due to lack of data on prevalence of CVD, the incidences are calculated on the basis of recorded events in HKS divided by the total regional population instead of the population free from CVD. Hence, the model will tend to underestimate the risk of primary events and consequently may tend to underestimate the life years gained from interventions. This is mainly a problem at higher ages: among participants in the Oslo Health Study 2000-2001, 29% of men and 20% of women 75 years old reported previous cardiovascular disease (stroke, angina, AMI). In age groups 60 years and younger the percentage was low and of minor importance.

4.2 LIMITATIONS

Guidelines for economic evaluation recommend that models have a life-long perspective (74). As mentioned in section 2.1, we ran the model until all individuals were dead or 100 years. The reason for stopping at 100 years was the lack of data on older people.

Patients are assumed to be on the primary prevention medication until the first cardiovascular event or until death. Hence all individuals on intervention will have a reduced mortality risk for the rest of their lives. A substantial proportion of the individuals will be on primary prevention for decades before they experience a CVD event. It should be noted that the clinical trials that we use to model intervention effectiveness seldom run for more than 3-5 years, but we assume that the reduced mortality risk last for the rest of the individual's life. It should be noted that if we only accounted for reduced mortality risk of 3-5 years, the life year gain would seldom be more than a few weeks. Here, the model reflects practice to not stop with these kinds of medications when one has started taking them. It is easy to explore in the model the impact of using medications for shorter periods of time.

The validation process proved that the input to the model need to be somewhat adjusted to fit Norwegian mortality data. This is a limitation of the model, which might be more consistent if it was based on fewer data sources, (use Framingham risk equations in stead of several data sources). However, we considered the use of old data from the US to be likely to give more bias, and hence kept the different sources.

The restricted number of events and health states represents a simplification of real life, but the inclusion of more states would entail need for data that only could be based on assumptions. A more complicated model would introduce health states that are less well documented in the literature, and hence more uncertainty would be introduced. Also, we would lack data on efficacy or effectiveness from high quality trials. The impact of omitting such (possibly rare) health states is unlikely to have much impact on the results, simply because

they are rare. One simplification is the omission of cardiac arrhythmias. Even though arrhythmias are common, they are omitted in our model. The most serious consequences of arrhythmias are death, heart failure and stroke, and these events are thoroughly covered in the NorCaD model, both in terms of costs and health outcome. The omission of peripheral vascular disease (intermittent claudication), will bias the health benefit from interventions to the extent that such interventions (*e.g.* smoke cessation) reduces the risk of peripheral vascular disease.

The model does not encompass combination of health states such as heart failure and stroke sequelae. Presumably, the model capture the true number of events that lead to potential combined health states, and the costs of the events would in principle be correct. In practice, however, a smaller proportion of patients are in the health states than the model would predict (the health states are "spread over too many patients"). To the extent the costs of combined states is different from the sum of the costs of each individual state, the model cost predictions are biased. Also, to the extent the health related quality of life (HRQOL) detriments from combined states is different from the sum of the individual detriments, the model predictions would be biased. Unfortunately, very little data are available of such combined effects, but the biases introduced are unlikely to be substantial.

The transition probabilities were based on clinical trials or register data. Because the most severe cases often are excluded from trials, the probabilities of moving to other health states are probably underestimated. By assumption, we multiplied all rates from clinical trials by 1.5 (1 and 2 in sensitivity analyses) in order to avoid bias in parameter values. The relative difference between RCT's and registry data are assumed to be the same over time.

The probabilities of new events after AMI is based on data gathered in the period 1990-2005. Hence some of the sources are based on old criteria for defining an AMI, while other sources are based on new criteria. How this might affect our model is not certain. When, in the future, data are available on all new events based on the new criteria, this will be an improvement of the model.

When collecting data from different sources, there is always a possibility of discrepancy between the data. For instance is the risk of stroke after angina (table 8), substantially higher than the risk of stroke after AMI and earlier stroke that had no sequelae (table 7 and 9). Even though this might seem counter-intuitive and may produce bias, we would introduce even more bias by assuming that one of them is more correct than the other.

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Appendix

A.1 ABBREVIATIONS AND ACRONYMS

CVD	Cardiovascular disease
PCI	Percutaneous coronary intervention
QALY	Quality adjusted life-year
AMI	Acute myocardial infarction
CDC	Centers for disease control and prevention
CHD	Coronary heart disease
RCT	Randomised controlled trial
EuroHeart	Euro Heart Survey
GRACE	The global registry of acute coronary events
SSB	Statistisk sentralbyrå (eng: Statistics Norway)
HUNT	Helseundersøkelsen i Nord-Trøndelag
HKS	Hjerte-, kar-, og slagregisteret - Helseregion vest
STEMI	ST-elevated myocardial infarction
SCORE	Systematic coronary risk evaluation
SBP	Systolic blood pressure
BMI	Body mass index
NOKC	Norwegian Knowledge Centre for the Health Services
HUBRO	The Oslo Health Study
OPPHED	Helseundersøkelsen i Oppland og Hedmark
TROFINN	Helseundersøkelsen i Troms og Finnmark
FRISC II	The Fragmin and Fast revascularisation during instability in coronary artery disease II trial
ICTUS	The invasive versus conservative treatment in unstable coronary syndromes
SMM	The former Senter for medisinsk metodevurdering (Norwegian Centre for Health Technology Assessment), now a part of NOKC
DES	Drug eluting stents
NCCHTA	National Coordinating Centre for Health Technology Assessment
SAVE	The Survival and Ventricular Enlargement trial
SOLVD	The Studies of Left Ventricular Dysfunction
TTO	Time trade-off

SG	Standard gamble
15D	15 Dimensions (utility instrument with 15 dimensions, developed by Harri Sintonen)
DRG	Diagnosis related groups
NOK	Norwegian Kroner

A.2 INCIDENCES OF CARDIOVASCULAR DISORDERS

All incidences are annual disease frequencies. For AMI Heart failure and stroke, these are based on registry data (HKS (16) and Innherred Stroke Registry (17)), for angina, the data are based on a prospective Norwegian cohort study (14).

	AMI (16)		Stroke (17)		Heart failure (16)		Angina (14)	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00016	0.00012
31	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00022	0.00013
32	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00027	0.00013
33	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00032	0.0001
34	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00037	0.00015
35	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00042	0.00015
36	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00048	0.00016
37	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00053	0.00017
38	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00058	0.00018
39	0.00041	0.00007	0.00013	0.00011	0.00011	0.00004	0.00063	0.00018
40	0.00160	0.00043	0.00013	0.00011	0.00030	0.00016	0.00068	0.00019
41	0.00160	0.00043	0.00013	0.00011	0.00030	0.00016	0.00083	0.00029
42	0.00160	0.00043	0.00013	0.00011	0.00030	0.00016	0.00099	0.00039
43	0.00160	0.00043	0.00013	0.00011	0.00030	0.00016	0.00113	0.00049
44	0,00160	0,00043	0,00013	0,00011	0,00030	0,00016	0,00127	0,00059
45	0,00160	0,00043	0,00060	0,00019	0,00030	0,00016	0,00142	0,00069
46	0,00160	0,00043	0,00060	0,00019	0,00030	0,00016	0,00157	0,00080
47	0,00160	0,00043	0,00060	0,00019	0,00030	0,00016	0,00172	0,00090
48	0,00160	0,00043	0,00060	0,00019	0,00030	0,00016	0,00186	0,00100
49	0,00160	0,00043	0,00060	0,00019	0,00030	0,00016	0,00201	0,00110
50	0,00372	0,00101	0,00060	0,00019	0,00136	0,00057	0,00216	0,00120
51	0,00372	0,00101	0,00060	0,00019	0,00136	0,00057	0,00255	0,00146
52	0,00372	0,00101	0,00060	0,00019	0,00136	0,00057	0,00294	0,00171
53	0,00372	0,00101	0,00060	0,00019	0,00136	0,00057	0,00333	0,00197
54	0,00372	0,00101	0,00060	0,00019	0,00136	0,00057	0,00372	0,00223
55	0,00372	0,00101	0,00223	0,00209	0,00136	0,00057	0,00411	0,00248
56	0,00372	0,00101	0,00223	0,00209	0,00136	0,00057	0,00450	0,00274
57	0,00372	0,00101	0,00223	0,00209	0,00136	0,00057	0,00489	0,00300
58	0,00372	0,00101	0,00223	0,00209	0,00136	0,00057	0,00528	0,00326
59	0,00372	0,00101	0,00223	0,00209	0,00136	0,00057	0,00567	0,00351
60	0,00734	0,00248	0,00223	0,00209	0,00505	0,00199	0,00606	0,00377
61	0,00734	0,00248	0,00223	0,00209	0,00505	0,00199	0,00629	0,00417
62	0,00734	0,00248	0,00223	0,00209	0,00505	0,00199	0,00651	0,00456
63	0,00734	0,00248	0,00223	0,00209	0,00505	0,00199	0,00673	0,00495
64	0,00734	0,00248	0,00223	0,00209	0,00505	0,00199	0,00696	0,00535
65	0,00734	0,00248	0,00727	0,00701	0,00505	0,00199	0,00718	0,00574
66	0,00734	0,00248	0,00727	0,00701	0,00505	0,00199	0,00740	0,00614
67	0,00734	0,00248	0,00727	0,00701	0,00505	0,00199	0,00763	0,00653

68	0,00734	0,00248	0,00727	0,00701	0,00505	0,00199	0,00785	0,00693
69	0,00734	0,00248	0,00727	0,00701	0,00505	0,00199	0,00808	0,00732
70	0,01204	0,00759	0,00727	0,00701	0,01640	0,00982	0,00830	0,00772
71	0,01204	0,00759	0,00727	0,00701	0,01640	0,00982	0,00835	0,00777
72	0,01204	0,00759	0,00727	0,00701	0,01640	0,00982	0,00841	0,00781
73	0,01204	0,00759	0,00727	0,00701	0,01640	0,00982	0,00846	0,00786
74	0,01204	0,00759	0,00727	0,00701	0,01640	0,00982	0,00852	0,00791
75	0,01204	0,00759	0,01994	0,01697	0,01640	0,00982	0,00857	0,00796
76	0,01204	0,00759	0,01994	0,01697	0,01640	0,00982	0,00863	0,00801
77	0,01204	0,00759	0,01994	0,01697	0,01640	0,00982	0,00868	0,00806
78	0,01204	0,00759	0,01994	0,01697	0,01640	0,00982	0,00874	0,00810
79	0,01204	0,00759	0,01994	0,01697	0,01640	0,00982	0,00879	0,00815
80	0,02069	0,01602	0,01994	0,01697	0,03926	0,03166	0,00884	0,00820
81	0,02069	0,01602	0,01994	0,01697	0,03926	0,03166	0,00894	0,00756
82	0,02069	0,01602	0,01994	0,01697	0,03926	0,03166	0,00903	0,00691
83	0,02069	0,01602	0,01994	0,01697	0,03926	0,03166	0,00913	0,00627
84	0,02069	0,01602	0,01994	0,01697	0,03926	0,03166	0,00922	0,00562
85	0,02069	0,01602	0,03346	0,02882	0,03926	0,03166	0,00932	0,00498
86	0,02069	0,01602	0,03346	0,02882	0,03926	0,03166	0,00941	0,00434
87	0,02069	0,01602	0,03346	0,02882	0,03926	0,03166	0,00951	0,00369
88	0,02069	0,01602	0,03346	0,02882	0,03926	0,03166	0,00960	0,00305
89	0,02069	0,01602	0,03346	0,02882	0,03926	0,03166	0,00970	0,00240
90	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0,00979	0,00176
91	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
92	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
93	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
94	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
95	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
96	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
97	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
98	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
99	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0
100	0,03044	0,02484	0,03346	0,02882	0,06162	0,06298	0	0

A.3 MORTALITY FROM DIFFERENT DISEASES

Annual mortality rates are based on data from SSB.no (1).

	Total mortality (SSB)		Mortality from CVD (SSB I00-I99)	
Index	Men	Women	Men	Women
30	0,00054	0,00021	0,00003	0,00003
31	0,00078	0,00063	0,00003	0,00003
32	0,00071	0,00026	0,00011	0,00006
33	0,00113	0,00067	0,00008	0,00009
34	0,00122	0,00049	0,00020	0,00000
35	0,00071	0,00065	0,00014	0,00006
36	0,00094	0,00063	0,00020	0,00000
37	0,00139	0,00067	0,00017	0,00000
38	0,00139	0,00050	0,00012	0,00009
39	0,00155	0,00086	0,00027	0,00003
40	0,00136	0,00075	0,00024	0,00010
41	0,00128	0,00099	0,00028	0,00016
42	0,00160	0,00107	0,00036	0,00013
43	0,00156	0,00092	0,00040	0,00010
44	0,00223	0,00127	0,00044	0,00013
45	0,00214	0,00130	0,00037	0,00019
46	0,00193	0,00176	0,00069	0,00010
47	0,00246	0,00124	0,00064	0,00013
48	0,00262	0,00182	0,00090	0,00016
49	0,00248	0,00251	0,00039	0,00013
50	0,00364	0,00194	0,00064	0,00039
51	0,00399	0,00227	0,00122	0,00034
52	0,00401	0,00277	0,00144	0,00072
53	0,00421	0,00252	0,00109	0,00057
54	0,00510	0,00348	0,00145	0,00055
55	0,00517	0,00308	0,00137	0,00054
56	0,00606	0,00368	0,00225	0,00049
57	0,00647	0,00443	0,00163	0,00052
58	0,00702	0,00500	0,00242	0,00049
59	0,00731	0,00490	0,00262	0,00058
60	0,00911	0,00554	0,00292	0,00081
61	0,00918	0,00529	0,00307	0,00138
62	0,00950	0,00562	0,00369	0,00116
63	0,01112	0,00577	0,00401	0,00146
64	0,01309	0,00808	0,00459	0,00176
65	0,01397	0,00809	0,00547	0,00160
66	0,01615	0,00943	0,00634	0,00194
67	0,01861	0,00905	0,00651	0,00263

68	0,01891	0,01020	0,00812	0,00345
69	0,02116	0,01232	0,00892	0,00289
70	0,02435	0,01233	0,00928	0,00379
71	0,02771	0,01328	0,01151	0,00490
72	0,02857	0,01709	0,01296	0,00522
73	0,03139	0,01798	0,01458	0,00622
74	0,03661	0,01957	0,01729	0,00821
75	0,03787	0,02301	0,01925	0,00945
76	0,04360	0,02668	0,01946	0,01099
77	0,04832	0,03054	0,02350	0,01110
78	0,05187	0,03331	0,02563	0,01500
79	0,06121	0,03645	0,03359	0,01891
80	0,07451	0,04472	0,03437	0,02097
81	0,08497	0,04860	0,03719	0,02444
82	0,09121	0,05542	0,04790	0,03268
83	0,09210	0,06262	0,05442	0,03206
84	0,11111	0,07399	0,05625	0,04271
85	0,11445	0,08130	0,06647	0,04540
86	0,13119	0,09038	0,07892	0,05548
87	0,14154	0,10517	0,07196	0,06264
88	0,17147	0,11980	0,09439	0,07292
89	0,18079	0,13788	0,10853	0,07773
90	0,18622	0,15420	0,11721	0,09113
91	0,21331	0,16908	0,12665	0,09842
92	0,24997	0,18875	0,13710	0,12242
93	0,24718	0,20382	0,14536	0,13591
94	0,28751	0,22751	0,15530	0,13820
95	0,27054	0,25164	0,19710	0,15288
96	0,37135	0,25058	0,17273	0,15767
97	0,38603	0,30334	0,17273	0,15767
98	0,24422	0,30428	0,17273	0,15767
99	0,28713	0,32270	0,17273	0,15767

A.4 AVERAGE LEVEL OF DIFFERENT RISK FACTORS FOR DIFFERENT DISEASES IN NORWAY

Data based on population studies in the period 2000-2003 (49-51, 53)

	Systolic blood pressure (mmHg)		Cholesterol (mmol/l)		Smoking (yes/no)		Diabetes (yes/no)		Percentage of
Index	Men	Women	Men	Women	Men	Women	Men	Women	men
30	126,9	114,8	5,16	4,88	0,27	0,28	0,008	0,007	50,20 %
31	127,1	115,3	5,22	4,93	0,28	0,29	0,008	0,007	50,77 %
32	127,3	115,8	5,27	4,98	0,28	0,30	0,008	0,007	50,66 %
33	127,5	116,2	5,32	5,02	0,29	0,30	0,008	0,007	50,53 %
34	127,8	116,7	5,37	5,07	0,29	0,31	0,008	0,007	50,68 %
35	128,0	117,2	5,41	5,12	0,30	0,32	0,008	0,007	50,78 %
36	128,3	117,8	5,46	5,17	0,30	0,32	0,008	0,007	50,91 %
37	128,6	118,3	5,50	5,21	0,31	0,33	0,008	0,007	50,81 %
38	128,8	118,9	5,54	5,26	0,31	0,33	0,008	0,007	51,30 %
39	129,1	119,4	5,58	5,30	0,31	0,34	0,008	0,007	51,27 %
40	129,4	120,0	5,62	5,34	0,32	0,34	0,018	0,011	51,29 %
41	129,8	120,6	5,65	5,39	0,32	0,34	0,018	0,011	50,66 %
42	130,1	121,3	5,68	5,43	0,32	0,35	0,018	0,011	51,10 %
43	130,4	121,9	5,72	5,47	0,32	0,35	0,018	0,011	51,04 %
44	130,8	122,5	5,75	5,51	0,32	0,35	0,018	0,011	50,95 %
45	131,2	123,2	5,77	5,55	0,33	0,35	0,018	0,011	51,08 %
46	131,6	123,9	5,80	5,59	0,33	0,35	0,018	0,011	50,75 %
47	132,0	124,6	5,82	5,63	0,33	0,35	0,018	0,011	50,64 %
48	132,4	125,3	5,84	5,67	0,33	0,35	0,018	0,011	50,51 %
49	132,8	126,0	5,86	5,71	0,33	0,35	0,018	0,011	50,77 %
50	133,2	126,8	5,88	5,74	0,32	0,35	0,035	0,019	50,60 %
51	133,7	127,5	5,90	5,78	0,32	0,34	0,035	0,019	50,51 %
52	134,1	128,3	5,91	5,82	0,32	0,34	0,035	0,019	50,83 %
53	134,6	129,1	5,92	5,85	0,32	0,34	0,035	0,019	51,23 %
54	135,1	129,9	5,93	5,89	0,32	0,33	0,035	0,019	51,01 %
55	135,6	130,7	5,94	5,92	0,31	0,33	0,035	0,019	50,95 %
56	136,1	131,5	5,95	5,95	0,31	0,32	0,035	0,019	51,10 %
57	136,6	132,4	5,95	5,99	0,31	0,32	0,035	0,019	50,62 %
58	137,1	133,2	5,96	6,02	0,30	0,31	0,035	0,019	50,73 %
59	137,7	134,1	5,96	6,05	0,30	0,30	0,035	0,019	50,54 %
60	138,2	135,0	5,96	6,08	0,29	0,29	0,057	0,032	50,67 %
61	138,8	135,9	5,95	6,11	0,29	0,29	0,057	0,032	50,27 %
62	139,4	136,8	5,95	6,14	0,28	0,28	0,057	0,032	49,79 %
63	140,0	137,8	5,94	6,17	0,28	0,27	0,057	0,032	49,25 %
64	140,6	138,7	5,93	6,20	0,27	0,26	0,057	0,032	49,40 %
65	141,2	139,7	5,92	6,22	0,27	0,25	0,057	0,032	48,73 %
66	141,8	140,7	5,91	6,25	0,26	0,24	0,057	0,032	48,28 %

67	142,5	141,7	5,90	6,28	0,25	0,23	0,057	0,032	48,07 %
68	143,1	142,7	5,88	6,30	0,25	0,22	0,057	0,032	47,82 %
69	143,8	143,7	5,86	6,33	0,24	0,21	0,057	0,032	46,61 %
70	144,5	144,8	5,84	6,35	0,23	0,20	0,083	0,076	46,79 %
71	145,1	145,8	5,82	6,37	0,23	0,19	0,083	0,076	46,85 %
72	145,8	146,9	5,80	6,40	0,22	0,18	0,083	0,076	46,10 %
73	146,6	148,0	5,77	6,42	0,21	0,17	0,083	0,076	45,34 %
74	147,3	149,1	5,74	6,44	0,20	0,16	0,083	0,076	45,26 %
75	148,0	150,2	5,71	6,46	0,20	0,15	0,083	0,076	44,76 %
76	148,8	151,3	5,68	6,48	0,19	0,14	0,083	0,076	43,44 %
77	149,6	152,5	5,65	6,50	0,18	0,13	0,083	0,076	42,95 %
78	149,6	152,5	5,65	6,50	0,18	0,13	0,083	0,076	42,32 %
79	149,6	152,5	5,65	6,50	0,18	0,13	0,083	0,076	41,33 %
80	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	40,21 %
81	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	39,06 %
82	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	37,21 %
83	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	35,92 %
84	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	35,13 %
85	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	34,46 %
86	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	32,73 %
87	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	30,79 %
88	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	29,21 %
89	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	28,38 %
90	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	27,70 %
91	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	27,07 %
92	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	24,38 %
93	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	23,50 %
94	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	22,50 %
95	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	22,07 %
96	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	18,99 %
97	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	19,06 %
98	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	21,08 %
99	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	19,01 %
100	149,6	152,5	5,65	6,50	0,18	0,13	0,115	0,124	15,93 %

A.5 DEATH THE FIRST YEAR AFTER AMI

Mortality per year after AMI

Age	Mortality (1st year)*	RR of mortality (later years)**
30-59	4%	3.55
60-69	9%	2.36
70-79	20%	1.00
80->	38%	1.00

*Data based on Swedish official numbers (26)

**Relative risk of death per year after AMI compared to the general population. Data calculated based on Dickstein 2006, Madsen 2005, Swedish official data (26) and Norwegian death rates (1)

Mortality more than one year after AMI, was based on Dickstein 2006 and Madsen 2005, which both had about 3 years follow-up. Both studies had probability of death close to 14% during follow-up. Because the average age in these studies was in the mid-60s, we compared this rate with the mortality from the Swedish report in the age group 60-69 years. We assumed that these data came from similar populations, and hence 9% of the 14% are assumed to die during the first year. The remaining two years of the follow-up, 5% of the cohort will then have died. We assumed similar death rates the second and third year after AMI, and hence 2.5% were assumed to die each remaining year.

To get a similar probability of death for the age group 30-59 years, we assumed a similar relationship between the age groups as in the Swedish official data. Hence the probability of death for this age group was assumed to be 2.5% X 4% / 9% = 1.1%

These data were then computed into rates based on the Norwegian official death rates for the given age groups. In the model these rates were applicated to the death rates in order to give age-adjusted death rates. For values 70 and above, the relative mortality risk was assumed to be the same as for disease-free.

A.6 DEATH FROM AMI, HEART FAILURE AND STROKE BEFORE HOSPITAL

Based on the HKS registry, the table shows the mortality rates per year. Rates are based on HKS and Norwegian official death register.

	Death before hospital	
Age	Men	Women
30-39 years	0.004 %	0.001 %
40-49 years	0.012 %	0.006 %
50-59 years	0.042 %	0.018 %
60-69 years	0.099 %	0.033 %
70-79 years	0.301 %	0.189 %
80-89 years	1.181 %	1.050 %
>90 years	4.566 %	4.156 %

A.7 RELATIVE RISK OF DEATH FOR DIFFERENT AGE GROUPS

Table A.7 Relative risk of dying with elevated cholesterol and blood pressure level from CHD and stroke for different age groups

	Cholesterol (per 1 mmol/L)		Systolic blood pressure (per 20 mmHg)	
Age	CHD	Stroke	CHD	Stroke
30-39	1.64	1.02	1,85	1,81
40-49	1,44	1,02	1,58	1,76
50-59	1,27	1,02	1,43	1,55
60-69	1,17	1,00	1,31	1,35
70-79	1,09	1,00	1,20	1,24
80-89	1,08	1,00	1,06	1,07
SCORE	1,27	1,02	1,43	1,55

Based on relative risk of death from SCORE, we adjusted for different age groups based on studies by Selmer (75) and Prospective Studies Collaboration (54).

A.8 COST DATA

Table A.8 Costs and cost components

Number of services Proportion of patients	Type of service	DRG-weight (where applicable)	Unit cost	Total
One attack of angina				
1	DRG 112	1,30	39 423	39 423
0,2	DRG 107	4,05	122 816	24 563
0,2	DRG 140	0,50	15 163	3 033
3	GP visit		264	792
2	GP test: ECG+cholesterol		108	216
1	Outpatient incl exerc. Test		4 143	4 143
0,5	9 months clopidrogrel 75 mg per day			5 325
	Total			77 494
Annual cost of being asymptomatic after MI				
2	GP visit		264	528
2	GP lab tests		108	216
1	ASA, statin, beta-blocker, ACE-inhibitor		2 236	2 236
	Total			2 980
Annual cost of being asymptomatic after stroke or angina				
2	GP visit		264	528
2	GP lab tests		108	216
1	ASA, statin, ACE-inhibitor		1 419	1 419
	Total			2 163
Cost of fatal AMI				
1	GP home visit		264	264
0,5	DRG 121	1,84	55 798	27 899
0,5	DRG 123	0,38	11 524	5 762
1	Ground ambulance		9 500	9 500
	Total			43 425
Cost of getting heart failure (event)				
1	GP visits		980	980
1	GP lab tests		108	108
0,2	Outpatient clinic visits incl full cardiolog.exam.		4 143	829
0,8	DRG 127	1,23	37 300	29 840
	Total			31 756
Cost of deterioration of heart failure				

1	GP visit		294	294
1	GP lab tests		108	108
0,8	DRG 127	1,23	37 300	29 840
0,2	Outpatient clinic visits incl full cardiolog.exam.		4 143	829
	Total			31 071
One year cost of heart failure				
0,5	DRG 127	1,23	37 300	18 650
2	Outpatient clinic visit		4 143	8 287
3	GP visit		264	792
3	GP lab tests		108	324
	ASA + statin+ ACE-inhibitor + diuretics + beta blocker + aldosteron antagonist			2 722
	Total			30 774
One year cost of moderate stroke sequelae				
1	Total care costs (Fjærtoft et.al. (59))		49 200	49 200
	Total			49 200
Cost of AMI in hospitals with PCI facilities				
1	Ground ambulance		9 500	9 500
1	GP visit		264	264
0,5	DRG112E (AMI+PCI without complications)	1,66	50 340	25 170
0,5	DRG112F (AMI+PCI with complications)	1,93	58 527	29 264
	Total			64 197
Cost of AMI in hospitals without PCI facilities				
1	Ground ambulance		9 500	9 500
1	GP visit		264	264
0,5	DRG122(AMI without complications)	1,06	32 145	16 072
0,5	DRG121 (AMI with complications)	1,84	55 798	27 899
1,8	Ground ambulance		9 500	17 100
0,45	DRG112E (AMI+PCI without complications)	1,66	50 340	22 653
0,45	DRG112F (AMI+PCI with complications)	1,93	58 527	26 337
0,9	DRG122(AMI without complications)	1,06	32 145	28 930
	Total			148 755
Average cost of AMI				
0,4	Hospital with PCI facilities		64 197	25 679
0,6	Hospital without PCI facilities		148 755	89 253
	Total			114 932
Cost of one year nursing home (the only difference between moderate and severe stroke sequelae)				
	Nursing home 1 year (Statistics Norway)			500 000
	Total			500 000
Cost of reinfarction				

0,33	DRG 121	1,84	55 798	18 413
0,33	DRG 122	1,06	32 145	10 608
0,33	DRG 123	0,38	11 524	3 803
	ASA, statin, beta blocker, ACE-inhibitor 90 days		2 236	551
	Clopidogrel 90 days		5 206	1 283
	Total			34 658

Cost of getting stroke (first year)	
One year of treatment for stroke (59)	164 000
Total	164 000

A.9 PROBABILITY DISTRIBUTIONS

In this appendix, we have included lists of parameters (with uncertainty) that were incorporated into the model as probability distributions.

Probability

Probability of AMI first year after angina for men	Beta, Integer parameters only, n = 1760, r = 27; Expected value: 0,015340909
Probability of AMI first year after angina for women	Beta, Integer parameters only, n = 1271, r = 22; Expected value: 0,017309205
Probability of heart failure first year after angina for men	Beta, Integer parameters only, n = 1760, r = 27; Expected value: 0,015340909
Probability of heart failure first year after angina for women	Beta, Integer parameters only, n = 1271, r = 23; Expected value: 0,018095987
Probability of stroke first year after angina for men	Beta, Integer parameters only, n = 1760, r = 21; Expected value: 0,011931818
Probability of stroke first year after angina for women	Beta, Integer parameters only, n = 1271, r = 14; Expected value: 0,011014949
Probability of a heart failure to last for 6-12 months	Beta, Real-numbered parameters, alpha = ((,5^2)*(1-,5)/(,05^2)), beta = (,5*(1-,5)/(,05^2))-((,5^2)*(1-,5)/(,05^2)); Expected value: 0,5
Probability of Angina after non-STEMI (unadjusted)	Beta, Integer parameters only, n = 1200, r = 108; Expected value: 0,09
Probability of heart failure the first year after non-STEMI	Beta, Integer parameters only, n = 6041, r = 1484; Expected value: 0,245654693
Probability of reinfarction after non-STEMI	Beta, Integer parameters only, n = 5367, r = 75; Expected value: 0,013974287
Probability of stroke 6mo after non-STEMI	Beta, Integer parameters only, n = 10522, r = 185; Expected value: 0,017582209
Probability of stroke in hospital after non-STEMI	Beta, Integer parameters only, n = 10522, r = 92; Expected value: 0,008743585
Probability of heart failure the first 6 months after reinfarction	Beta, Real-numbered parameters, alpha = 847, beta = 2329; Expected value: 0,266687657
Probability of angina after STEMI	Beta, Real-numbered parameters, alpha = 115, beta = 894; Expected value: 0,113974232
Probability of heart failure after STEMI	Beta, Integer parameters only, n = 6625, r = 1905; Expected value: 0,28754717
Probability of reinfarction after STEMI	Beta, Integer parameters only, n = 4431, r = 120; Expected value: 0,027081923
Probability of stroke within 6 months after STEMI	Beta, Integer parameters only, n = 12911, r = 266; Expected value: 0,020602587
Probability of stroke in hospital after STEMI	Beta, Integer parameters only, n = 12911, r = 163; Expected value: 0,012624894
Probability of moderate sequelae the first year after stroke	Beta, Integer parameters only, n = 25175, r = 1813; Expected value: 0,072015889
Probability of severe sequelae the first year after a stroke	Beta, Integer parameters only, n = 25175, r = 4255; Expected value: 0,169016882

Relative risks

Relative risk of CHD with diabetes for men	Log-Normal, u (mean of logs) = 0,684598, sigma (std dev of logs) = 0,08; Expected value: 1,989330202
Relative risk of CHD with diabetes for women	Log-Normal, u (mean of logs) = 1,126971, sigma (std dev of logs) = 0,15; Expected value: 3,121210789
Decreasing risk over time	exp(ln(ABriskRelAll)*(rrDecrAge^(ageTr-60)))
Relative risk of angina with ACE-inhibitors compared to diuretics	Log-Normal, u (mean of logs) = 0,093651, sigma (std dev of logs) = 0,03631; Expected value: 1,098900581

Effect of ACE-inhibitors on angina compared to placebo	Log-Normal, u (mean of logs) = -0,062535, sigma (std dev of logs) = 0,35; Expected value: 0,998715825
Relative risk of angina with ACE-inhibitor compared to CCB	Log-Normal, u (mean of logs) = 0,06766, sigma (std dev of logs) = 0,04262; Expected value: 1,070973697
Relative risk of dying with ACE-inhibitor compared to CCB	Log-Normal, u (mean of logs) = 0,04879, sigma (std dev of logs) = 0,03178; Expected value: 1,050530195
Relative risk of HF with ACE inhibitor compared to CCB	Log-Normal, u (mean of logs) = -0,16252, sigma (std dev of logs) = 0,04760; Expected value: 0,850962583
Relative risk of AMI with ACE-inhibitor compared to CCB	Log-Normal, u (mean of logs) = 0,00995, sigma (std dev of logs) = 0,03035; Expected value: 1,01046494
Relative risk of stroke with ACE-inhibitor compared to CCB	Log-Normal, u (mean of logs) = 0,13976, sigma (std dev of logs) = 0,05544; Expected value: 1,151766438
Relative risk of death with ACE-inhibitors compared to diuretics	Log-Normal, u (mean of logs) = -0,010411, sigma (std dev of logs) = 0,03035; Expected value: 0,990098903
Effect of ACE-inhibitors on death compared to placebo	Log-Normal, u (mean of logs) = 0,151347, sigma (std dev of logs) = ,28026; Expected value: 1,209999364
Relative risk of heart failure with ACE-inhibitors compared to diuretics	Log-Normal, u (mean of logs) = 0,138153, sigma (std dev of logs) = 0,04705; Expected value: 1,14942274
Effect of ACE-inhibitors on heart failure compared to placebo	Log-Normal, u (mean of logs) = -0,062535, sigma (std dev of logs) = 0,35; Expected value: 0,998715825
Relative risk of non-STEMI with ACE-inhibitors compared to diuretics	Log-Normal, u (mean of logs) = 0,019793, sigma (std dev of logs) = 0,02852; Expected value: 1,02040509
Effect of ACE-inhibitors on AMI compared to placebo	Log-Normal, u (mean of logs) = -0,062535, sigma (std dev of logs) = 0,35; Expected value: 0,998715825
Relative risk of stroke with ACE-inhibitors compared to diuretics	Log-Normal, u (mean of logs) = 0,126490, sigma (std dev of logs) = 0,05177; Expected value: 1,136359881
Effect of ACE-inhibitors on stroke compared to placebo	Log-Normal, u (mean of logs) = -0,482953, sigma (std dev of logs) = ,36724; Expected value: 0,659996735
Relative risk of death after AMI	Log-Normal, u (mean of logs) = 1,241991, sigma (std dev of logs) = 0,2232; Expected value: 3,549831438
Relative risk of death after AMI	Log-Normal, u (mean of logs) = 0,848844, sigma (std dev of logs) = ,1453; Expected value: 2,361743329
Relative risk of death after AMI	Log-Normal, u (mean of logs) = 0,675950, sigma (std dev of logs) = 0,1100; Expected value: 1,977829438
Relative risk of death after AMI	Log-Normal, u (mean of logs) = 0,111719, sigma (std dev of logs) = ,1989; Expected value: 1,140537457
Relative risk of death after AMI	Log-Normal, u (mean of logs) = 0,625791, sigma (std dev of logs) = ,2232; Expected value: 1,916882407
Relative risk of death after AMI	Normal, Mean = ,8594, Std Dev = ,1453; Expected value: 0,8594
Relative risk of AMI after angina	Log-Normal, u (mean of logs) = 1,278581, sigma (std dev of logs) = 0,2438; Expected value: 3,699879383
Relative risk of AMI after angina compared to well	Log-Normal, u (mean of logs) = 2,414622, sigma (std dev of logs) = 0,2603; Expected value: 11,57097775
Relative risk of angina with ARB compared to diuretics	Log-Normal, u (mean of logs) = 0,15700, sigma (std dev of logs) = 0,07590; Expected value: 1,173370533
Relative risk of death with ARB compared to diuretics	Log-Normal, u (mean of logs) = 0,0198, sigma (std dev of logs) = 0,04742; Expected value: 1,021144777
Relative risk of heart failure with ARB compared to diuretics	Log-Normal, u (mean of logs) = -0,12783, sigma (std dev of logs) = 0,05476; Expected value: 0,88132337
Relative risk of non-STEMI with ARB compared to diuretics	Log-Normal, u (mean of logs) = 0,15700, sigma (std dev of logs) = 0,07590; Expected value: 1,173370533
Relative risk of stroke with ARB compared to diuretics	Log-Normal, u (mean of logs) = 0,13103, sigma (std dev of logs) = 0,08052; Expected value: 1,143703562
Relative risk of angina with ASA compared to placebo	Log-Normal, u (mean of logs) = -0,062535, sigma (std dev of logs) = 0,35; Expected value: 0,998715825
Relative risk of death with ASA compared to placebo	Log-Normal, u (mean of logs) = -0,062605, sigma (std dev of logs) = 0,03807; Expected value: 0,939995362
Relative risk of heart failure with ASA compared to placebo	Log-Normal, u (mean of logs) = -0,062535, sigma (std dev of logs) = 0,35; Expected value: 0,998715825
Relative risk of non-STEMI with ASA compared to placebo	Log-Normal, u (mean of logs) = -0,254979, sigma (std dev of logs) = 0,11418; Expected value: 0,780000698
Relative risk of stroke with ASA compared to placebo	Log-Normal, u (mean of logs) = -0,044427, sigma (std dev of logs) = 0,08493; Expected value: 0,960001485
Relative risk of Angina with beta blockers	Log-Normal, u (mean of logs) = -0,023858, sigma (std dev of logs) = 0,09009; Expected value: 0,980394835
Effect of beta blockers on angina compared to placebo	Log-Normal, u (mean of logs) = -0,065180, sigma (std dev of logs) = ,08124; Expected value: 0,93999565
Relative risk of angina with beta blockers vs. ARB	Log-Normal, u (mean of logs) = -0,12222, sigma (std dev of logs) = 0,11453; Expected value: 0,890776754
Relative risk of dying with beta blockers compared to ARB	Log-Normal, u (mean of logs) = 0,11653, sigma (std dev of logs) = 0,06592; Expected value: 1,126035124
Relative risk of heart failure with beta blockers vs. ARB's	Log-Normal, u (mean of logs) = 0,05129, sigma (std dev of logs) = 0,11223; Expected value: 1,059278257
Relative risk of AMI with beta blocker vs. ARB	Log-Normal, u (mean of logs) = -0,04879, sigma (std dev of logs) = 0,10145; Expected value: 0,957294743
Relative risk of stroke with beta blocker compared to ARB	Log-Normal, u (mean of logs) = 0,28768, sigma (std dev of logs) = 0,08526; Expected value: 1,338185556
Relative risk of dying with beta blockers	Log-Normal, u (mean of logs) = -0,081360, sigma (std dev of logs) = 0,09381; Expected value: 0,925927036
Effect of Beta blockers on death compared to placebo	Log-Normal, u (mean of logs) = -0,001994, sigma (std dev of logs) = 0,06315; Expected value: 0,999999961
Relative risk of heart failure with beta blockers	Log-Normal, u (mean of logs) = 0,332382, sigma (std dev of logs) = 0,27813; Expected value: 1,449270242
Effect of beta blockers on heart failure compared to placebo	Log-Normal, u (mean of logs) = -0,062535, sigma (std dev of logs) = 0,35; Expected value: 0,998715825
Relative risk of non-STEMI with beta blockers	Log-Normal, u (mean of logs) = -0,023858, sigma (std dev of logs) = 0,09009; Expected value: 0,980394835
Effect of beta blockers on AMI compared to placebo	Log-Normal, u (mean of logs) = -0,065180, sigma (std dev of logs) = ,08124; Expected value: 0,93999565
Relative risk of stroke with beta blockers	Log-Normal, u (mean of logs) = 0,195861, sigma (std dev of logs) = 0,17239; Expected value: 1,234566821

Effect of beta blockers on stroke compared to placebo	Log-Normal, u (mean of logs) = -0,280076, sigma (std dev of logs) = ,10617; Expected value: 0,759997629
Relative risk of angina with CCB and ACE compared to diuretics and beta blockers	Log-Normal, u (mean of logs) = -0,131308, sigma (std dev of logs) = 0,08340; Expected value: 0,880002773
Relative risk of death with CCB and ACE compared to diuretics and beta blockers	Log-Normal, u (mean of logs) = -0,106515, sigma (std dev of logs) = 0,04806; Expected value: 0,900000358
Relative risk of heart failure with CCB and ACE compared to diuretics and beta blockers	Log-Normal, u (mean of logs) = -0,181198, sigma (std dev of logs) = 0,11703; Expected value: 0,840002854
Relative risk of non-STEMI with CCB and ACE compared to diuretics and beta blockers	Log-Normal, u (mean of logs) = -0,129038, sigma (std dev of logs) = 0,04916; Expected value: 0,880003277
Relative risk of stroke with CCB and ACE compared to diuretics and beta blockers	Log-Normal, u (mean of logs) = -0,263984, sigma (std dev of logs) = 0,07244; Expected value: 0,770003497
Relative risk of angina with CCB compared to diuretics	Log-Normal, u (mean of logs) = -0,000742, sigma (std dev of logs) = 0,03853; Expected value: 1,00000028
Effect of CCB on angina compared to placebo	Log-Normal, u (mean of logs) = -0,276585, sigma (std dev of logs) = ,17450; Expected value: 0,770003765
Relative risk of death with CCB compared to diuretics	Log-Normal, u (mean of logs) = -0,020252, sigma (std dev of logs) = 0,03005; Expected value: 0,980394244
Effect of CCB on death compared to placebo	Log-Normal, u (mean of logs) = -0,191680, sigma (std dev of logs) = ,10344; Expected value: 0,829999581
Relative risk of heart failure with CCB compared to diuretics	Log-Normal, u (mean of logs) = 0,313506, sigma (std dev of logs) = 0,04908; Expected value: 1,369862573
Effect of CCB on heart failure compared to placebo	Log-Normal, u (mean of logs) = -0,352029, sigma (std dev of logs) = ,21693; Expected value: 0,720003153
Relative risk of non-STEMI with CCB compared to diuretics	Log-Normal, u (mean of logs) = 0,009571, sigma (std dev of logs) = 0,03096; Expected value: 1,010100934
Effect of CCB on AMI compared to placebo	Log-Normal, u (mean of logs) = -0,276585, sigma (std dev of logs) = ,17450; Expected value: 0,770003765
Relative risk of stroke with CCB compared to diuretics	Log-Normal, u (mean of logs) = -0,059921, sigma (std dev of logs) = 0,05746; Expected value: 0,943395032
Effect of CCB on stroke compared to placebo	Log-Normal, u (mean of logs) = -0,643210, sigma (std dev of logs) = ,12907; Expected value: 0,529998837
Relative risk of events decreasing by age	0,978
Relative risk of Angina with diuretics	Log-Normal, u (mean of logs) = -0,306029, sigma (std dev of logs) = 0,53574; Expected value: 0,849998813
Relative risk of Dying with Diuretics	Log-Normal, u (mean of logs) = -0,220078, sigma (std dev of logs) = 0,13681; Expected value: 0,810001231
Relative risk of heart failure diuretics	Log-Normal, u (mean of logs) = -0,684359, sigma (std dev of logs) = 0,14845; Expected value: 0,51000217
Relative risk of non-STEMI with diuretics	Log-Normal, u (mean of logs) = -0,154250, sigma (std dev of logs) = 0,08282; Expected value: 0,860002121
Relative risk of stroke with diuretics	Log-Normal, u (mean of logs) = -0,585765, sigma (std dev of logs) = 0,10904; Expected value: 0,559999079
Relative risk of AMI in year 2-4 after heart failure for men	Log-Normal, u (mean of logs) = 0,183602, sigma (std dev of logs) = 0,47; Expected value: 1,341853678
Relative risk of AMI in year 2-4 after heart failure for women	Log-Normal, u (mean of logs) = 1,235509, sigma (std dev of logs) = 0,42; Expected value: 3,757331508
Proportion of deaths due to cardiovascular disease	0,92
Relative risk of dying from heart failure later years (women)	Log-Normal, u (mean of logs) = 0,822505, sigma (std dev of logs) = ,3813; Expected value: 2,447824926
Relative risk of dying from heart failure first year (men)	Log-Normal, u (mean of logs) = 2,465228, sigma (std dev of logs) = ,1206; Expected value: 11,852042078
Relative risk of dying from heart failure second year (men)	Log-Normal, u (mean of logs) = 1,600145, sigma (std dev of logs) = ,1916; Expected value: 5,045517776
Relative risk of dying from heart failure third year (men)	Log-Normal, u (mean of logs) = 1,509380, sigma (std dev of logs) = ,1996; Expected value: 4,614945599
Relative risk of dying from heart failure the first year after AMI	Log-Normal, u (mean of logs) = 2,756848, sigma (std dev of logs) = ,0889; Expected value: 15,812481634
Relative risk of dying from heart failure later years (men)	Log-Normal, u (mean of logs) = 0,707709, sigma (std dev of logs) = ,3162; Expected value: 2,133364306
Relative risk of dying from heart failure first year (women)	Log-Normal, u (mean of logs) = 2,402329, sigma (std dev of logs) = ,1488; Expected value: 11,171877912
Relative risk of dying from heart failure second year (women)	Log-Normal, u (mean of logs) = 1,887229, sigma (std dev of logs) = ,1488; Expected value: 6,674536209
Relative risk of dying from heart failure third year (women)	Log-Normal, u (mean of logs) = 2,014371, sigma (std dev of logs) = ,1768; Expected value: 7,614087272
Relative risk of stroke when having heart failure compared to well	Log-Normal, u (mean of logs) = 1,854878, sigma (std dev of logs) = ,353653; Expected value: 6,803336967
Relative risk of worsening compared to incidence of heart failure	Log-Normal, u (mean of logs) = 2,259692, sigma (std dev of logs) = 0,028898; Expected value: 9,584139025
Relative risk of heart failure after stroke compared to well	Log-Normal, u (mean of logs) = 0,630612, sigma (std dev of logs) = 0,35365302; Expected value: 2,000000097
Relative risk of AMI with moderate stroke sequelae compared to when well	Log-Normal, u (mean of logs) = 1,477348, sigma (std dev of logs) = 0,118018; Expected value: 4,411929509
Relative risk of dying with moderate stroke sequelae compared to asymptomatic	Log-Normal, u (mean of logs) = 0,691024, sigma (std dev of logs) = 0,07; Expected value: 2,000653746
Relative risk of new stroke when having moderate stroke sequelae compared to when well	Log-Normal, u (mean of logs) = 1,458448, sigma (std dev of logs) = 0,041915; Expected value: 4,303060155

Relative risk of AMI after AMI compared to after well	Log-Normal, u (mean of logs) = 1,073792, sigma (std dev of logs) = 0,290677; Expected value: 3,052736981
Relative risk of angina after AMI compared to after well	Log-Normal, u (mean of logs) = 3,066959, sigma (std dev of logs) = 0,142322; Expected value: 21,695107534
Relative risk of stroke after AMI compared to when well	Log-Normal, u (mean of logs) = 1,008881, sigma (std dev of logs) = 0,130315; Expected value: 2,765916375
Relative risk of AMI after angina compared to when well (men)	Log-Normal, u (mean of logs) = 0,134823, sigma (std dev of logs) = 0,189273; Expected value: 1,165016365
Relative risk of AMI after angina compared to when well (women)	Log-Normal, u (mean of logs) = 1,328601, sigma (std dev of logs) = 0,233752; Expected value: 3,880333093
Relative risk of angina after angina compared to when well	Log-Normal, u (mean of logs) = 2,417087, sigma (std dev of logs) = 0,13868; Expected value: 11,321494321
Relative risk of dying after angina compared to well	Log-Normal, u (mean of logs) = 0,205065, sigma (std dev of logs) = 0,09; Expected value: 1,232586738
Relative risk of stroke after angina compared to well	5,34
Relative risk of stroke after angina for women	5,26
Relative risk of AMI after stroke compared to when well	Log-Normal, u (mean of logs) = 1,216862, sigma (std dev of logs) = 0,280263; Expected value: 3,5118244
Relative risk of dying after TIA compared to well	Log-Normal, u (mean of logs) = 1,585761, sigma (std dev of logs) = 0,1117057; Expected value: 4,913566642
Proportion of deaths due to CVD	0,72
Relative risk of stroke after stroke compared to when well	Log-Normal, u (mean of logs) = 1,022458, sigma (std dev of logs) = 0,166821; Expected value: 2,818972968
Relative risk of events in real life compared to RCT's	Log-Normal, u (mean of logs) = 0,403893, sigma (std dev of logs) = 0,06; Expected value: 1,500341877
Relative risk of dying from reinfarction compared to well	Log-Normal, u (mean of logs) = 3,326045, sigma (std dev of logs) = 0,2423; Expected value: 28,657054551
Relative risk of dying with severe compared to moderate stroke sequelae	Log-Normal, u (mean of logs) = 0,000000, sigma (std dev of logs) = 0,0000001; Expected value: 1
Relative risk of angina with statin	Log-Normal, u (mean of logs) = -0,163407, sigma (std dev of logs) = ,04211; Expected value: 0,849998772
Relative risk of dying with statin	Log-Normal, u (mean of logs) = -0,073215, sigma (std dev of logs) = 0,03591; Expected value: 0,930000425
Relative risk of heart failure with statin	Log-Normal, u (mean of logs) = -0,084634, sigma (std dev of logs) = ,05007; Expected value: 0,920001022
Relative risk of non-STEMI with statin	Log-Normal, u (mean of logs) = -0,261910, sigma (std dev of logs) = 0,03318; Expected value: 0,77000402
Relative risk of stroke with statins	Log-Normal, u (mean of logs) = -0,187260, sigma (std dev of logs) = 0,04313; Expected value: 0,829999732
Relative risk of CVD events after Stroke compared to after AMI	1
Relative risk of stroke with diabetes compared to without	Log-Normal, u (mean of logs) = 1,615459, sigma (std dev of logs) = 0,41; Expected value: 5,471260343
Relative risk of dying after stroke compared to well	Log-Normal, u (mean of logs) = 2,486994, sigma (std dev of logs) = ,0348; Expected value: 12,032357991
Relative risk of stroke for various tobacco use	Log-Normal, u (mean of logs) = 0,596368, sigma (std dev of logs) = 0,26015244; Expected value: 1,878000498
Relative risk of CHD with tobacco use	Log-Normal, u (mean of logs) = 0,666255, sigma (std dev of logs) = 0,29580297; Expected value: 2,034000815
Adjustment for probabilities measured after 6 months	Log-Normal, u (mean of logs) = 0,389831, sigma (std dev of logs) = 0,17682651; Expected value: 1,499999549
Adjustment for probabilities that are observed in hospital	Log-Normal, u (mean of logs) = 0,677513, sigma (std dev of logs) = 0,17682651; Expected value: 1,999999254

Costs and related parameters

Cost of one year with ACE-inhibitors	Gamma, alpha = (467,2^2)/(233,6^2), lambda = 467,2/(233,6^2); Expected value: 467,2
Cost of ALAT	15
Cost per year with aldosteronantagonist	Gamma, alpha = (361,35^2)/(180,675^2), lambda = 361,35/(180,675^2); Expected value: 361,35
Cost per ground ambulance turn-out	Gamma, alpha = (9500^2)/(4750^2), lambda = 9500/(4750^2); Expected value: 9500
Cost of getting angina and be treated	nAngDRG112*wDRG112*cDRG+nAngDRG107*wDRG107*cDRG+nAngDRG140*wDRG140*cDRG+nAngGPvisit*cGPvisit+nAngGPtest*cGPtest+nAngOutpatient*cOutpatient+nAngClopid*cClopidogrel
Annual wage rate industrial worker	Gamma, alpha = (341300^2)/(4750^2), lambda = 341300/(4750^2); Expected value: 341300
Cost of one year with ASA	Gamma, alpha = 4,00, lambda = 0,0145730; Expected value: 274,480203115
Cost of ASAT	15
Cost of having asymptomatic CVD for a year	nAsyGPvisit*cGPvisit+nAsyGPtest*cGPtest+cACE+cStatin+cASA+If(track_AMI=1;cBetablockers;0)
Costs related to use of beta blockers after MI	Gamma, alpha = 4,00, lambda = 0,0048924; Expected value: 817,594636579
Cost of CK	15
Costs of one year with clopidogrel	Gamma, alpha = 4,00, lambda = 0,0007683; Expected value: 5206,299622543
Cost of diuretics per year in control arm	cIntDiuretics
Cost of Diuretics and beta blocker per year	cConDiur+cIntBetablockers
Extra cost of GP visit when on medication	0
Cost of creatinine	15

Cost of dying a cardiac death	nDieGPvisit*cGPvisit+nDieDRG121*wDRG121*cDRG+nDieDRG122*wDRG122*cDRG+nDieDRG123*wDRG123*cDRG+nDieAmb*cAmbulance
Cost per year of diuretics	Gamma, alpha = 4,00, lambda = 0,0322321; Expected value: 124,099888
Cost per DRG weight	30325
Cost of electrolytes	45
Cost of GP visits first year with statins	3*(cGPvisit+cALAT+cASAT+cLDLchol+cHDLchol+cCK+cTrigl+cInnsending701a)
Cost of GP visits later years with statins	cGPstatinFirstYear/2
Cost of GP test (ECG+cholesterol)	108
Cost of GP visits first year with thiazides	3*(cGPvisit+cElectrolytes+cCreatinin+cLDLchol+cHDLchol+cCK+cTrigl+cInnsending701a)
Cost of GP visits later years with thiazides	cGPthiazidFirstYear/2
Cost of GP visit	264
Cost of HDL cholesterol	39
Fullstendig kardiologisk undersøkelse (takst A02)	294
Cost of GP visit at first heart failure	980
Short term costs of getting heart failure	nHFsGPvisit*cHFGPvisitNew+nHFsGPtest*cGPtest+nHFsOutpatient*cOutpatient+nHFsDRG127*wDRG127*cDRG
Cost of worsening of heart failure	nHFwGPvisit*cHFGPvisit+nHFwGPtest*cGPtest+nHFwDRG127*wDRG127*cDRG+nHFwOutpatient*cOutpatient
Cost of a year with heart failure	nHFyDRG127*wDRG127*cDRG+nHFyOutpatient*cOutpatient+nHFyGPvisit*cGPvisit+nHFyGPtest*cGPtest+cASA+cStatin+cACE+cDiuretics+cBetablockers+cAldo
Cost of hypothetical intervention	0
Indirect costs related to death	cProdLoss/2
Cost of Innsending (701a)	47
Cost of a year with ACE-inhibitors	Gamma, alpha = 4,00, lambda = 0,0116252; Expected value: 344,080101848
Cost of a year with ARB-treatment (16 mg)	Gamma, alpha = 4,00, lambda = 0,0018947; Expected value: 2111,152161292
Cost of Albyl-E 75 mg	Gamma, alpha = 4,00, lambda = 0,0145629; Expected value: 274,670566989
Cost of a year of beta blocker treatment	Gamma, alpha = 4,00, lambda = 0,0127816; Expected value: 312,949865432
Cost of a year with CCB	Gamma, alpha = 4,00, lambda = 0,0031603; Expected value: 1265,702623169
Cost of CCB+ACE (Nifedipine 30mg + Lisinopril 20 mg)	cIntCCB+cIntACE
Cost of a year of diuretics treatment	Gamma, alpha = 4,00, lambda = 0,0132009; Expected value: 303,009643282
Extra cost for GP visits when on medication	If((AAicControl=1)&(AAiControl=0);(cGPthiazidFirstYear*(_stage=0)+cGPthiazidLaterYears*(_stage<>0));0)
Cost of a year with statin treatment	Gamma, alpha = 4,00, lambda = 0,0078178; Expected value: 511,652894676
Cost of LDL cholesterol	39
Cost of having moderate stroke sequelae	Gamma, alpha = 4,00, lambda = 0,0000813; Expected value: 49200,49200492
Costs related to a non-ST-elevated myocardial infarction	cStemi
Cost of one year in a nursing home with severe stroke sequelae	Gamma, alpha = 4,00, lambda = 0,0000080; Expected value: 500000
Cost per outpatient visit (incl. exerc. test)	4143
Cost of one year production loss	cAnnWage*pPayrollTax
Cost of reinfarction	nReinfDRG121*wDRG121*cDRG+nReinfDRG122*wDRG122*cDRG+nReinfDRG123*wDRG123*cDRG+(cASA+cStatin+cClopidogrel+cBetablockers+cACE)*nReinfClop/365,25
Cost of one year with statins	Gamma, alpha = 4,00, lambda = 0,0059088; Expected value: 676,956404008
Costs related to ST-elevated MI	(nStemiGPvisit*cGPvisit+nStemiIntAmb*cAmbulance+nStemiIntDRG123*wDRG123*cDRG+nStemiIntDRG106*wDRG106*cDRG+nStemiIntDRG112e*wDRG112e*cDRG+nStemiIntDRG112f*wDRG112f*cDRG)*0,4+(nStemiOthGPvisit*cGPvisit+nStemiOthAmb*cAmbulance+nStemiOthDRG123*wDRG123*cDRG+nStemiOthDRG121*wDRG121*cDRG+nStemiOthDRG122*wDRG122*cDRG+nStemiOthDRG112e*wDRG112e*cDRG+nStemiOthDRG112f*wDRG112f*cDRG)*0,6
Costs of getting stroke	Gamma, alpha = 4,00, lambda = 0,0000244; Expected value: 163934,426229508
Cost of triglycerides	15

Units of Clopidogrel per angina	1
Number of DRG107 with angina	Beta, Integer parameters only, n = 100, r = 20; Expected value: 0,2
Number of DRG112 with angina	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of DRG 140 with angina	Beta, Integer parameters only, n = 100, r = 20; Expected value: 0,2
Number of GP tests (ECG+cholesterol) with angina	Gamma, alpha = 4, lambda = 2; Expected value: 2
Number of GP visits with angina	Gamma, alpha = 3, lambda = 1; Expected value: 3
Number of outpatient visits (incl. exerc. test) with angina	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of GP tests with Asymptomatic CVD	Gamma, alpha = 4, lambda = 2; Expected value: 2
Number of GP visits with asymptomatic CVD	Gamma, alpha = 4, lambda = 2; Expected value: 2
Number of ground ambulances needed related to cardiovascular death	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of DRG121 when cardiac death	Beta, Integer parameters only, n = 100, r = 50; Expected value: 0,5
Number of DRG 122 related to cardiovascular death	0
Number of DRG 123 when cardiovascular death	Beta, Integer parameters only, n = 100, r = 50; Expected value: 0,5
Number of GP visits related to cardiac deaths	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of DRG 127 when getting heart failure	Beta, Integer parameters only, n = 100, r = 80; Expected value: 0,8
Number of GP lab tests when getting heart failure	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of GP visits when getting heart failure	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of outpatient visits when getting heart failure	Beta, Integer parameters only, n = 100, r = 20; Expected value: 0,2
Number of DRG 127 when getting worsening of heart failure	Beta, Integer parameters only, n = 100, r = 80; Expected value: 0,8
Number of GP tests with worsening of heart failure	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of GP visits with worsening of heart failure	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of outpatient visits with worsening of heart failure	Beta, Integer parameters only, n = 100, r = 20; Expected value: 0,2
Number of DRG 127 per year with heart failure	Beta, Integer parameters only, n = 100, r = 50; Expected value: 0,5
Number of GP lab tests per year with heart failure	Gamma, alpha = 3, lambda = 1; Expected value: 3
Number of GP visits per year with heart failure	Gamma, alpha = 3, lambda = 1; Expected value: 3
Number of outpatient visits per year with heart failure	Gamma, alpha = 4, lambda = 2; Expected value: 2
Number of days with clopidogrel after reinfarction	Gamma, alpha = 4, lambda = 0,04444444; Expected value: 90,000009
Number of DRG 121 with reinfarction	Beta, Integer parameters only, n = 100, r = 33; Expected value: 0,33
Number of DRG 122 with reinfarction	Beta, Integer parameters only, n = 100, r = 33; Expected value: 0,33
Number of DRG 123 with reinfarction	Beta, Integer parameters only, n = 100, r = 33; Expected value: 0,33
Number of GP visits with STEMI at intervention hospital	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of Ground ambulances when STEMI at intervention hospital	Gamma, alpha = 4, lambda = 4; Expected value: 1
Number of DRG 106 when STEMI at intervention hospital	0
Number of DRG 112E when STEMI at intervention hospital	Beta, Integer parameters only, n = 100, r = 50; Expected value: 0,5
Number of DRG 112F when STEMI at intervention hospital	Beta, Integer parameters only, n = 100, r = 50; Expected value: 0,5
Number of DRG 123 when STEMI at intervention hospital	0
Number of ambulances with STEMI at other hospitals	Gamma, alpha = 2,8, lambda = 1; Expected value: 2,8
Number of DRG 112e when STEMI at other hospitals	Beta, Integer parameters only, n = 100, r = 45; Expected value: 0,45
Number of DRG 112f when STEMI at other hospitals	Beta, Integer parameters only, n = 100, r = 45; Expected value: 0,45
Number of DRG 121 when STEMI at other hospitals	Beta, Integer parameters only, n = 100, r = 50; Expected value: 0,5
Number of DRG 122 when STEMI at other hospitals	Gamma, alpha = 4,2, lambda = 3; Expected value: 1,4
Number of DRG 123 when STEMI at other hospitals	0
Number of GP visits when STEMI without PCI facilities	1
Weight for DRG 106	Gamma, alpha = 4, lambda = 0,79840319; Expected value: 5,010000023
Weight for DRG 107	Gamma, alpha = 4, lambda = 0,98765432; Expected value: 4,050000004
Weight for DRG 112	Gamma, alpha = 4, lambda = 3,0769; Expected value: 1,30000975

Weight for DRG 112E	Gamma, alpha = 4, lambda = 2,409638554; Expected value: 1,66
Weight for DRG 112f	Gamma, alpha = 4, lambda = 2,07253886; Expected value: 1,93
Weight for DRG 121	Gamma, alpha = 4, lambda = 2,1739; Expected value: 1,84001104
Weight for DRG 122	Gamma, alpha = 4, lambda = 3,7736; Expected value: 1,05999576
Weight for DRG 123	Gamma, alpha = 4, lambda = 10,5263; Expected value: 0,38000057
Weight for DRG 127	Gamma, alpha = 4, lambda = 3,2520; Expected value: 1,2300123
Weight for DRG 140	Gamma, alpha = 4, lambda = 8; Expected value: 0,5
Adherence to Beta blocker therapy	Beta, Integer parameters only, n = 12286, r = 9008; Expected value: 0,733192251
Adherence to combination treatment (diuretics+betablockers)	Beta, Real-numbered parameters, alpha = ((0,982221^2)*(1-0,982221)/(0,001347^2)), beta = (0,982221*(1-0,982221)/(0,001347^2))-((0,982221^2)*(1-0,982221)/(0,001347^2)); Expected value: 0,982221
Adherence in placebo-arm	Beta, Integer parameters only, n = 61074, r = 46285; Expected value: 0,757851131
Adherence to ACE-inhibitors compared to CCB's	Log-Normal, u (mean of logs) = -0,072812, sigma (std dev of logs) = 0,021958; Expected value: 0,929999786
Adherence to ACE-inhibitors compared to thiazides	Log-Normal, u (mean of logs) = 0,061639, sigma (std dev of logs) = 0,021724; Expected value: 1,063829322
Adherence to ACE-inhibitors	Log-Normal, u (mean of logs) = -0,280734, sigma (std dev of logs) = ,509728; Expected value: 0,860000178
Adherence to ARB treatment	Log-Normal, u (mean of logs) = -0,211698, sigma (std dev of logs) = 0,044203; Expected value: 0,809999987
Adherence to ARBs compared to CCB's	Log-Normal, u (mean of logs) = 0,048436, sigma (std dev of logs) = 0,026623; Expected value: 1,050000239
adherence to ASA in trials	Log-Normal, u (mean of logs) = 0,262238, sigma (std dev of logs) = 0,175466; Expected value: 1,320000557
Adherence to CCB-treatment when compared to placebo	Beta, Real-numbered parameters, alpha = ((0,883425^2)*(1-0,883425)/(0,001773^2)), beta = (0,883425*(1-0,883425)/(0,001773^2))-((0,883425^2)*(1-0,883425)/(0,001773^2)); Expected value: 0,883425
Adherence to combination treatment (CCB+ACE)	Beta, Real-numbered parameters, alpha = ((0,987447^2)*(1-0,987447)/(0,001134^2)), beta = (0,987447*(1-0,987447)/(0,001134^2))-((0,987447^2)*(1-0,987447)/(0,001134^2)); Expected value: 0,987447
Adherence to CCB's compared to placebo	Log-Normal, u (mean of logs) = ,012374, sigma (std dev of logs) = ,121886; Expected value: 1,019999461
adherence to diuretics treatment	Log-Normal, u (mean of logs) = -0,063051, sigma (std dev of logs) = 0,048481; Expected value: 0,939999631
Adherence to statin therapy	Log-Normal, u (mean of logs) = -0,116682, sigma (std dev of logs) = 0,017205; Expected value: 0,889999842