Cost-based optimisation of chronic heart disease interventions

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ABSTRACT

Title: Cost-based optimisation of chronic heart disease interventions

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Coronary heart disease (CHD) is the leading cause of death by non-communicable diseases. The severity of CHD places a large economic strain on the individual, thus the need for preventative strategies. Personalising such strategies is beneficial for the patient and would prevent generalised treatment with a low cost-effectiveness.

Personalised cost-effective interventions were identified for two case studies. Blood tests were analysed to identify biomarkers indicating a high risk for CHD. Interventions affecting the biomarkers were identified and analysed using a Markov model. The model utilised four states to simulate the survivability of the patient. Cost parameters were added to the simulation to calculate the financial consequences of the interventions. Cost-effective interventions were identified based on the International $ quality adjusted life year (QALY) value at completion of the simulation.

Analysis of case study 1 and 2, identified thirteen and four interventions possibilities respectively. Of these, α-glucosidase inhibitors (6.80 QALY) and antidepressants (5.06 QALY) were found to be the most effective interventions for the respective case studies. The probability of remaining healthy in the case studies, after five years, increased with the use of these interventions (8% and 6%).

Current and previous CHD state of living contributes the most to the cost distribution of the model (89% and 86%). Costs for β-blockers (Int$ 33 663; case study 1) and biguanides (Int$ 23 254; case study 2) were the lowest at the end of the simulation. These interventions were also found to be the most cost-effective for the respective case studies.

It was recommended that β-blockers, diuretics or biguanides be considered as the most cost-effective interventions for case study 1. For case study 2, biguanides, antidepressants and statins were recommended as the most cost-effective preventative options.

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"*For I know the plans I have for you*", *declares the Lord, "plans to prosper you and not harm you, plans to give you hope and a future." – Jeremiah 29:11*

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LIST OF ABBREVIATIONS

Abbreviation	*Description*
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CHD	Coronary Heart Disease
CHOICE	CHOosing Interventions that are Cost-Effective
CPI	Consumer Price Index
CVD	Cardiovascular Disease
FDC	Fixed Dose Combination
GDP	Gross Domestic Product
HDL	High-density lipoprotein
ICER	Incremental Cost-Effectiveness Ratio
LY	Life Years
MPO	Myeloperoxidase
NDP	National Development Plan
NPV	Net Present Value
PPP	Purchasing Power Parities
PRR	Personal Relative Risk
QALE	Quality Adjusted Life Expectancy
QALY	Quality Adjusted Life Years
WHO	World Health Organization

NOMENCLATURE

Term	***Description***
ASSIGN	Scottish Intercollegiate Guidelines Network to assign preventative treatment CHD risk assessment model.
Biomarker	Measurable indicator of the severity or presence of some disease state.
cCHD	Costs expenditure when experiencing a CHD event.
cDeath	Cost expenditure when dying.
CHD	Disease in which plaque builds up inside the coronary arteries.
cHealthy	Yearly cost expenditures when being healthy.
Cohort	A population with a shared characteristic.
cPCHD	Cost expenditure for the subsequent years following a CHD event.
CVD	Diseases of the heart, blood vessels and circulatory system.
FDC	Fixed Dose Combination, Combination of more than one active pharmaceutical ingredient in a single tablet.
Int$	Hypothetical currency with the same purchasing power parity as the U.S. dollar in the United States at a given point in time.
$nDeath_x$	The risk of dying of non-CHD related causes in an age group.
pACHD	Probability of experiencing an additional CHD event after an initial event/s has been experienced.
pCHD	Probability of experiencing a CHD event in one year.
pDCHD	Probability of dying when experiencing a CHD event.
Polypill	See FDC.
PROCRAM	Prospective Cardiovascular Münster CHD risk model.
PRR	Patient-specific relative risk for CHD adjusted to the measured biomarkers.
QALY	One life year with perfect quality of living
qCHD	Quality of living in the year when experiencing a CHD event.
qHealthy	Quality of living while being healthy.
qPCHD	Quality of living after a CHD had been experienced.
QRESEARCH	QRISK1 and QRISK2 cardiovascular risk algorithms.
SCORE	Systematic Coronary Risk Evaluation and Reynolds score model
Serum	The liquid plasma component in blood that is neither a blood cell nor clotting factor, and does not include fibrinogens.

CHAPTER 1 - INTRODUCTION

1 Introduction

1.1 Preamble

1.1.1 Coronary heart disease

Cardiovascular diseases (CVD) are ranked as the leading cause of death in the world [1]. Deaths due to CVD accounted for almost a third of all deaths in 2013. The total number of cardiovascular deaths has increased and is possibly caused by ageing and growth in populations worldwide [2]. CVD are still not understood completely, even though several studies have been completed and new research is continuously being added to the field [3]–[6].

Coronary heart disease (CHD) is the most prevalent disease of the cardiovascular and circulatory diseases [7]. It accounts for 47% of CVD related deaths [1], thus showing that coronary heart disease is still not understood. This lack of understanding of the disease means that prevention measures cannot be implemented optimally. However, the ongoing research provides medical professionals, such as cardiologists, with improving new information to help prevent such diseases.

A decrease in CHD deaths has been seen in high income countries [1] due to increased awareness and diagnosis. The picture for the developing world however does not look that bright. In developing countries the number of CHD deaths is twice as many as those resulting from the prevalent infectious diseases HIV, tuberculosis and malaria combined [8]. Controlling these diseases is stressed throughout several studies and is highly prioritised in developing countries [9]. South Africa is classified as an upper middle income and developing country [10].

Of the total deaths (458 933) in South Africa in 2013, 76 468 were caused by diseases of the circulatory system. The deaths account for 16.7% of all deaths and increased from 16.2% in 2011. This is the second highest cause of death after infectious and parasitic diseases [11]. The reduction of deaths related to heart disease is included in the 2030 national development plan (NDP) and stresses the need for preventive measures [12]. Proactive prevention can only be achieved through the understanding of CHD and it is therefore important to look at the latest research.

One of the oldest and most frequently used risk predictive models is the Framingham heart study [4]. In this multivariable model, common risk factors are used: age, total cholesterol, HDL cholesterol, smoking status and systolic blood pressure [4]. These risk factors are

measured and a 10 year risk is calculated based on a point system [13]. The Framingham risk predictors are easily accessible, but lack dynamic properties for streamlining the risk prediction [14], [15].

A dynamic model with a larger number of available variables allows the user to generate a more precise risk prediction [15]. Dynamic risk prediction utilises a wider base of risk predictors that allow small variations to be accounted for. This accommodates the use of interventions that target specific factors to change the risk profile of an individual [15]. Such an integrated model was developed by Mathews *et al.* [16]–[18] by using serum biomarkers as measurement points.

The integrated model combines pathogenic and lifestyle factors to predict a patient's relative risk for CHD [16]. Lipid-related, inflammation, oxidative stress, coagulation, renal functions, vascular function and metabolic markers are used in the model [17]. Precise measurement of the biomarkers enables the model to be used for patient-specific risk prediction [16]. Changes in the marker levels due to interventions, provides a dynamic changing risk prediction.

Several other models are available for risk predictions. These models include: assessing cardiovascular risk to Scottish Intercollegiate Guidelines Network to assign preventative treatment (ASSIGN) score, QRESEARCH cardiovascular risk algorithms (QRISK1 and QRISK2), Prospective Cardiovascular Münster (PROCAM), systematic coronary risk evaluation (SCORE) and Reynolds score. The models are relatively similar and comparisons between them are affected by outcome selection and optimism biases [19].

The model developed by Mathews *et al.* [16]–[18] is used within this study. This model gives a highly dynamic risk prediction for an individual. CHD interventions can be patient-specifically prescribed and the effects can be measured. However, each intervention will have a different economic impact on the patient. Costs associated with each intervention vary widely and do not have the same cost-effectiveness. It is therefore important to look at the economic impact that the interventions would have on the individual.

1.1.2 Economic state of the health sector

In 2007 the world economy experienced a severe recession and financial crisis. The incident started in several advanced economy countries and rapidly spread to advanced-emerging and secondary-emerging economies [20]. The financial crisis impacted the health sector throughout the world and posed several threats [21]. Health expenditure decreased worldwide [22] and access to health care was restricted due to budget cuts.

The recession had several consequences that were not anticipated, including increased number of HIV infections and outbreaks of other infectious diseases [22]. Unforeseen consequences received most of the attention during the financial crisis and reduced the expenditure on CHD. The same trend for CHD expenditure during the financial crisis is visible in South Africa's health sector. CHD expenditure remained constant until 2010, while total expenditure annually increased. In 2011 CHD expenditure increased rapidly to counter act the zero growth of the previous years. [12]

South Africa's health expenditure has increased by 4.5% annually since 2007 [23]. An amount of US$ 30.2 billion was spend during the 2013/2014 financial year and relates to 8.3% of the gross domestic product (GDP) [24]. Costs of health care in South Africa are higher compared to other countries in the World Health Organization's (WHO) upper middle income group. Countries in this group spend on average 6.4% of GDP on health care [23], [25] . Even though the total expenditure increased over the past years, the burden on the individual has increased as well.

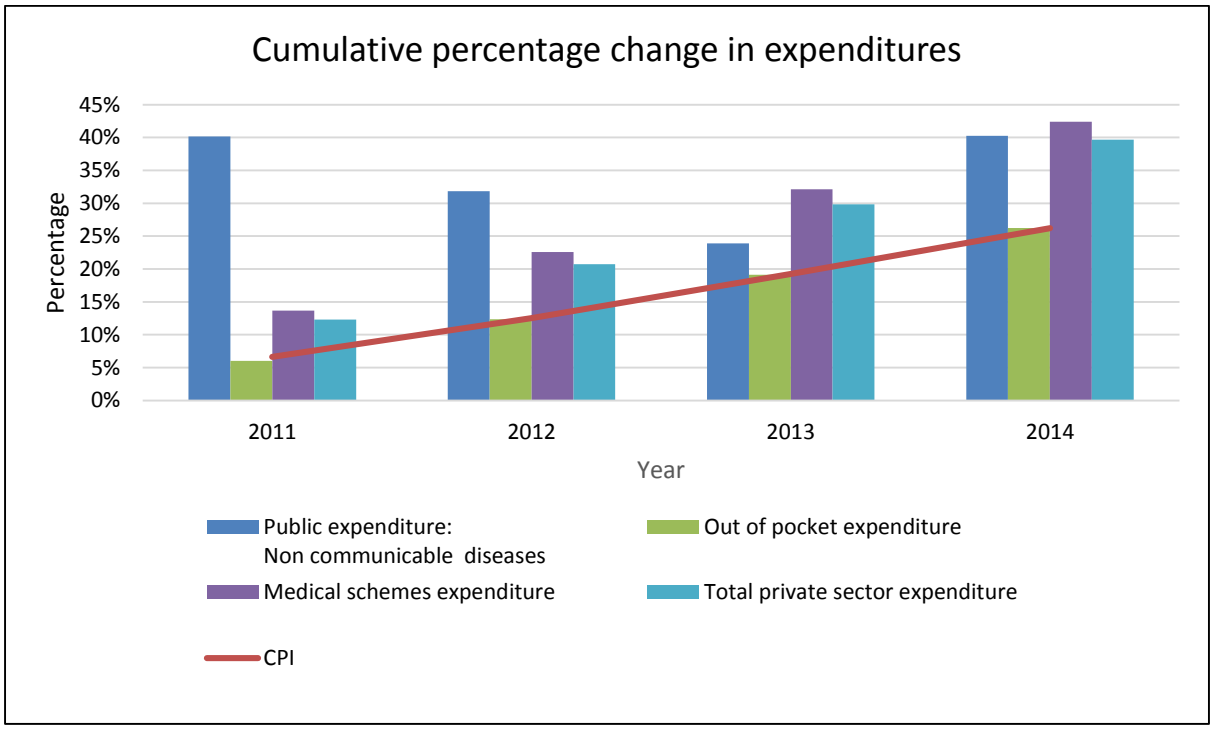


Figure 1: Public and private expenditure trends in South Africa since 2010-2014 [24], [26], [27]

The trends in expenditure since 2010 (Figure 1), show increases higher than the consumer price index (CPI). Public expenditure on non-communicable diseases, which includes CHD, increased to 40.2% in 2011 before decreasing annually. During 2014, it increased to 40.3%

cumulative growth since 2010 and finished the same as in 2011. This phenomenon is due to the counter acting of a rapid increase of 38% on expenditure towards communicable diseases during the financial crisis [26].

Post-recession disease outbreaks were prioritised and received greater funding to contain the situations [9]. Funding models were revised and changed due to the increase of non-communicable deaths in South Africa [11]. As public funding decreased, the private sector started paying larger amounts towards health care. Expenditure on health care by the private sector increased by about 40% over the past five years [27].

One of the main contributors of this expenditure is the expenses paid by medical schemes. Medical schemes increased funding by 42.4% during the past five years. This is due to the increase in general costs of medical care [21]–[23]. Medical scheme tariffs impacted the individual with an increase of 42.2% over the same period [28]. Out of pocket costs for the individual followed the CPI over the years which would be considered normal.

Combining the increases in medical scheme fees and out of pocket expenditure escalates the costs for an individual above the CPI [9], [28]. Addressing the financial burden requires that costs should be assessed from an individual's perspective. Costs towards CHD are one of the categories with the highest expenditure for an individual or medical scheme [28]. It is therefore important that CHD expenditure should be reduced where possible, while maintaining the highest efficiency of prevention and treatment.

CHD cost contributors are mainly preventive interventions and hospitalisation costs during incidents [29]. Hospitalisation costs are only applicable for the individual or his/her funder, should he or she experience a CHD event. It is therefore difficult to reduce the costs of hospitalisation, but intervention costs could be limited. Recommending or prescribing the most cost-effective intervention will reduce the cost to the individual while ensuring that they receive the most beneficial care.

Collaboration between risk identification and cost evaluations provides a foundation for decisions on the most optimal way forward. This enables the individual to follow interventions which are both highly beneficial as well as cost effective. Using one of the risk models in conjunction with a cost analysis gives the opportunity to provide such recommendations.

1.2 Biomarkers for coronary heart disease

At the heart of CHD risk prediction using the model of Mathews *et al.* [16] are serum biomarkers. The biomarkers are used as indicators of a pathogenic pathway or underlying disorder, such as systemic inflammation [30], [31]. By measuring the specific biomarkers, a relative risk for CHD can be predicted, as associated with the markers [32]. The model enables the biomarkers to be linked to patient-specific pathogenic, lifestyle and pharmacotherapeutic factors.

Table 1: Salient serum and functional biomarkers of CHD and prospective ones

Biomarker (class and salient examples)	**Prediction of CHD Relative risk (95% CI)**	**Size of studies (N = number of trials, n = number of patients)**	**Ref.**
Lipid-related markers:			
Triglycerides	0.99 (0.94-1.05)	(*N* = 68, *n* = 302 430)	[33]
LDL	1.25 (1.18-1.33)	(*N* = 15, *n* = 233 455)	[34]
HDL	0.78 (0.74-0.82)	(*N* = 68, *n* = 302 430)	[33]
ApoB	1.43 (1.35-1.51)	(*N* = 15, *n* = 233 455)	[34]
Leptin	1.04 (0.92-1.17)	(*n* = 1 832)	[35]
Inflammation markers:			
hsCRP	1.20 (1.18-1.22)	(*N* = 38, *n* = 166 596)	[36]
IL-6	1.25 (1.19-1.32)	(*N* = 25, *n* = 42 123)	[37]
TNF-α	1.17 (1.09-1.25)	(*N* = 7, *n* = 6 107)	[37]
GDF-15	1.40 (1.10-1.80)	(*n* = 1 740)	[38]
OPG	1.41 (1.33-1.57)	(*n* = 5 863)	[39]
Marker of oxidative stress:			
MPO	1.17 (1.06-1.30)	(*n* = 2 861)	[40]
Marker of vascular function and neurohormonal activity:			
BNP	1.42 (1.24-1.63)	(*N* = 40, *n* = 87 474)	[41]
Homocysteine	1.15 (1.09-1.22)	(*N* = 20, *n* = 22 652)	[42], [43]
Coagulation marker:			
Fibrinogen	1.15 (1.13-1.17)	(*N* = 40, *n* = 185 892)	[36]
Necrosis marker:			
Troponins	1.15 (1.04-1.27)	(*n* = 3 265)	[44]
Renal function marker:			
Urinary ACR	1.57 (1.26-1.95)	(*n* = 626)	[45]
Metabolic markers:			
HbA_{1c}	1.42 (1.16-1.74)	(*N* = 2, *n* = 2 442)	[46]
IGF-1	0.76 (0.56-1.04)	(*n* = 3 967)	[47]
Adiponectin	0.97 (0.86-1.09)	(*N* = 14, *n* =21 272)	[48]
Cortisol	1.10 (0.97-1.25)	(*n* = 2 512)	[49], [50]
BDNF	**?**	**?**	[51]–[53]
Insulin resistance (HOMA)	1.46 (1.26-1.69)	(*N* = 17, *n* = 51 161)	[54]

From "How do high glycaemic load diets influence coronary heart disease?" by Mathews *et al.*[16]; n denotes number of participants; N, number of trials; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin–to-creatinine ratio; GDF-15, growth-differentiation factor-15; LDL, low-density lipoprotein; HbA1c, glycosylated haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostasis model assessment.

Found within most of the commonly used models are the conventional biomarkers that are used for CHD risk prediction. Of these, LDL, HDL and total cholesterol are the most prevalent markers used as indication for CHD risks [33]. However, as it is clear from Table 1, these biomarkers do not present the highest relative risk of the analysed biomarkers. Table 1 contains a list of biomarkers used within the integrated model of Mathews *et al.* [16] and the associated relative risk thereof, which is graphically shown in Figure 2.

Shown in Table 1, the prominent serum and functional biomarkers for CHD as well as prospective ones. Main biomarkers are grouped according to their serum classes. Relative risk for CHD of each marker is quoted along with a 95% certainty, as found in literature [16]. This is graphically indicated in the figure below in an ascending order. The number of trials and patients analysed are stated for the respective studies. Only the number of patients is indicated, if only one study formed part of the analysis.

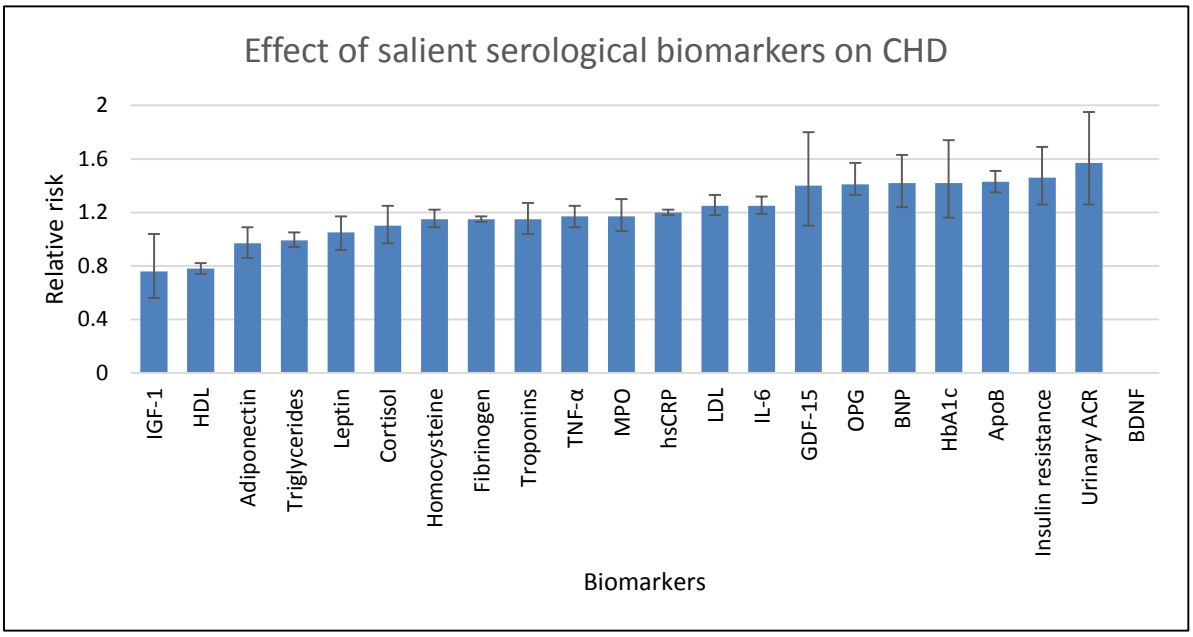


Figure 2: Relative risk of salient and functional biomarkers of CHD Adopted from "How do high glycaemic load diets influence coronary heart disease?" by Mathews *et al*. [16]; HDL, high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin-to-creatinine ratio; GDF-15, growth-differentiation factor-15; LDL, low-density lipoprotein; HbA_{1c}, glycated haemoglobin A_{1c}; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostasis model assessment.

From the table and figure it can be seen that each biomarker would affect the individual's relative risk differently. It is therefore important to analyse each of these markers individually and not to base predictions on a single marker. Individual biomarker analysis provides opportunities for interventions to be specifically chosen based on the results. The risk reduction process is accelerated due to the specific treatment [55].

The model used in the study utilises the serum biomarkers to quantify and characterise the system [16]. Integration between the biomarkers gives a descriptive view of the risk profile for the individual. Using this profile the hallmarks for CHD are identified and can be treated [16], [56]. Interventions affecting each biomarker and hallmark are limited in this study to those used within the model.

Biomarkers are analysed based on their relative risk and the influence that they have within the model. The profile created gives an indication of what interventions should be prescribed. Interventions can then be evaluated for their effectiveness and the fiscal impact that it would have on the individual.

1.3 Coronary heart disease interventions

Interventions for CHD are used to prevent future incidents by reducing the relative risk in an individual. Interventions range from surgical procedures to lifestyle modification and pharmaceutical therapies [56]–[58]. Effectiveness, costs, treatment period and intrusion on quality of life are different for each group of interventions [57]. Considering the different types of available options widens the pool of possibilities as to what the optimal treatment is.

Interventions can be used for preventing either primary or secondary CHD events [58]–[60]. Primary and secondary prevention are not limited to certain groups of interventions and can be utilised in both instances [59]. Prevention strategies are primarily focussed on reducing the risk for hypercoagulability, hypercholesterolaemia, hyperglycaemia, inflammatory state and hypertension. These conditions are the generalised hallmarks of CHD and is not necessarily the root cause for a patient's condition [4]. The need still exists to follow the best intervention for the patient's individual situation. These interventions can be identified by using the integrated model in Figure 3 [16].

The model does not take surgery into account as a possible intervention, but incorporates health factors and pharmacotherapeutics. Health factors form the first layer of the model and indicate the effects that it has on certain tissues. Pathways are used to indicate the pathogenesis from the tissues to the hallmarks of CHD. These pathways shows how each of the factors, biomarkers and interventions interact with one another [16].

In this study the focus is placed on the biomarkers and interventions included within the model. The biomarkers are indicated with red flags () while pharmaceutical therapies are indicated with blue tags () in Figure 3. Both the biomarkers and pharmaceutical interventions are found within the pathogenesis layer of the model. Health factors influence the pathogeneses

in a limited manner. The model design allows only initial influences from and limited feedback to the health factors, thus restricting the influence of health factors on the biomarkers.

Quantification of the impact of the health factors is biased based on the individual's reference point [40], [61]. Differences in the reference bases and the lack of measurability procedures for the intensity of the health factor, complicate the ability to prescribe patient-specific interventions [40], [61]. Health factors are therefore excluded from the possible range of interventions due to the lack of quantification and lack of standardised reference points.

The focus of available treatments shifts to pharmaceutical agents by removing the surgical procedures and health factors as interventions. Clinical trials and studies give values that are used to predict the probability of CHD [62]. Evaluating these risk probabilities quantifies the benefit of each treatment group. Table 2 shows the pharmaceutical agents depicted in the model as well as the relative risk associated with each.

Pharmaceutical drugs are actively involved in the model and form the base for changes to the biomarkers [16]–[18]. Each drug upregulates or inhibits certain pathways in the model, affecting the pathogenesis. Pharmaceutical therapy is used to treat or control: blood pressure, cholesterol levels, blood coagulation factors, psychological issues and blood glucose and insulin resistance [59], [63]–[73]. Pathways by which the pharmaceutical agents work on the CHD hallmarks are shown in Table 2.

Pharmaceutical drugs are characterised in Table 2 according to their class. Studies with the above stated characteristics, with regard to number of trials and patients, were used to determine the relative risk of the drug class. Series of pathway routes that lead to the CHD hallmarks (A – E) are given in the second part of the table. One such route is the influence of statins acting on pathway 12 and ending at hypercholesterolemia via pathway 32. The model was used along with applicable literature to identify these routes by which the drugs would reach the hallmark.

Interventions follow a series of different pathways to reach the hallmarks. Every intervention that influences pathways is not used in practice, even though it would be able to reach a hallmark through the model. Table 2 shows which interventions are used in practice (✓), as well others that are proposed (**?**) for use. Proposed interventions give additional treatment opportunities for targeting specific biomarkers.

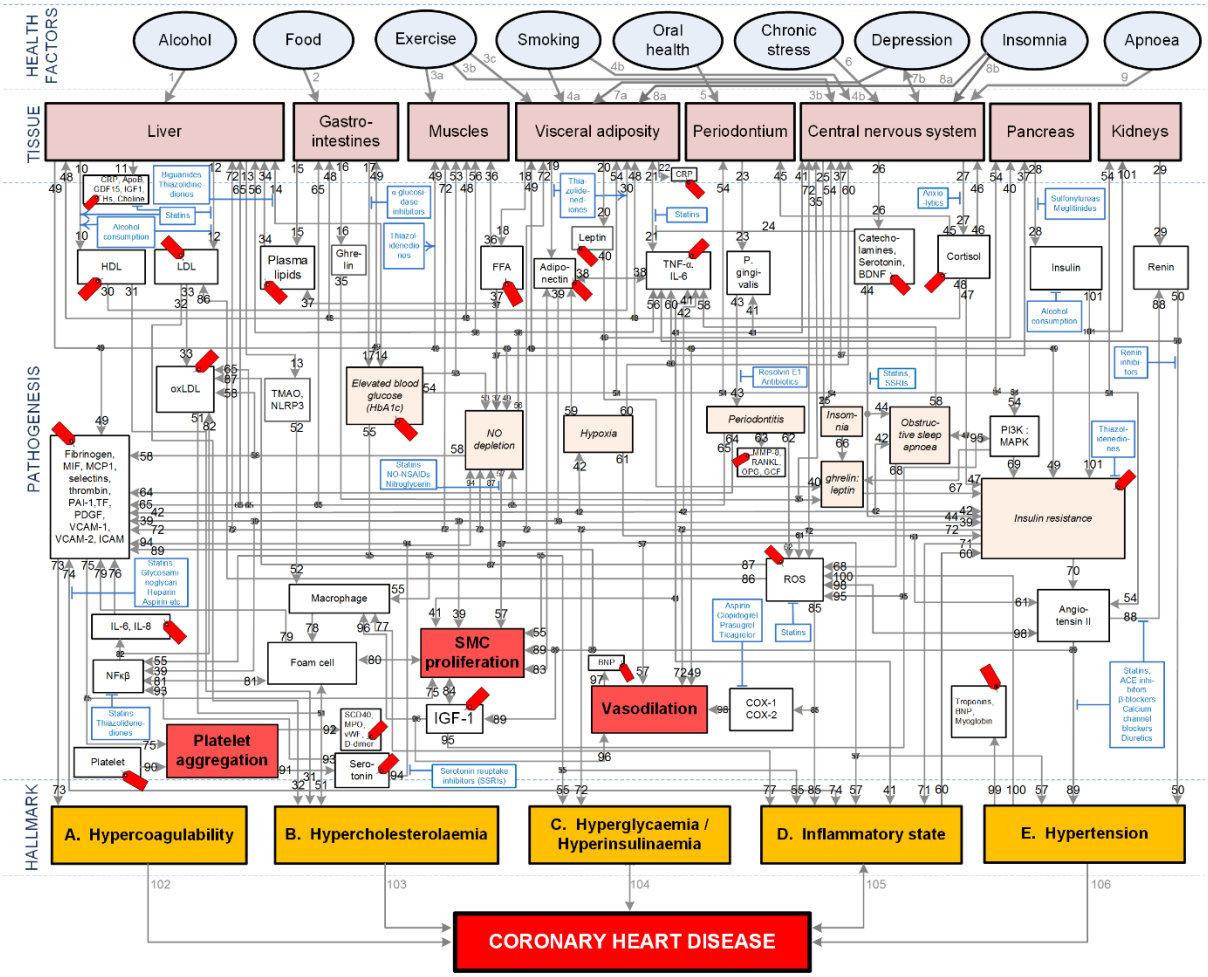


Figure 3: Integrated CHD model From "How do high glycaemic load diets influence coronary heart disease?" by Mathews *et al*. [16] HDL denotes high-density lipoprotein; LDL, low-density lipoprotein; oxLDL, oxidised LDL; FFA, free fatty acids; TMAO, an oxidation product of trimethylamine (TMA); NLRP3, Inflammasome responsible for activation of inflammatory processes as well as epithelial cell regeneration and microflora; Hs, homocysteine; IGF-1, insulin-like growth factor-1; TNF-α , tumour necrosis factor-α; IL, interleukin; NO, nitric oxide; NO-NSAIDs, combinational NO-non-steroidal anti-inflammatory drug; SSRI, selective serotonin reuptake inhibitors; ROS, reactive oxygen species; NFκβ, nuclear factor-κβ; SMC, smooth muscle cell; HbA1c, glycosylated haemoglobin A1c; P. gingivalis, Porphyromonas gingivalis; vWF, von Willebrand factor; PDGF, platelet-derived growth factor; MIF, macrophage migration inhibitory factor; SCD-40, recombinant human sCD40 ligand; MPO, myeloperoxidase; MMP, matrix metalloproteinase; VCAM, vascular cell adhesion molecule; ICAM, intracellular adhesion molecule; CRP, C-reactive protein; PAI, plasminogen activator inhibitor; TF, tissue factor, MCP, monocyte chemoattractant protein; BDNF, brain-derived neurotrophic factor; PI3K, phosphatidylinositol 3-kinase; MAPK, mitogen-activated protein (MAP) kinase; RANKL, receptor activator of nuclear factor kappa-beta ligand; OPG, osteoprotegerin; GCF, gingival crevicular fluid; D-dimer, fibrin degradation product D; BNP, B-type natriuretic peptide; ACE, angiotensin-converting-enzyme; COX, cyclooxygenase; β-blocker, beta-adrenergic antagonists

Table 2: Salient and prospective pharmaceutical agents for CHD

Drug class	Prediction of CHD RR (95% CI)	Study characteristics (N = number of trials, n = number of patients)	Ref.	A. Anti-hypercoagulability (Pathway #; status)	B. Anti-hypercholesterolemia (Pathway #; status)	C. Anti-hyperglycaemia/ hyperinsulinemia (Pathway #; status)	D. Anti-inflammatory (Pathway #; status)	E. Anti-hypertensive (Pathway #; status)	Ref.
Statins:	0.78 (0.76-0.80)	(*N* = 26, *n* = 169 138)	[63]	74-73; ✓	12-32; ✓	44-72 ✓	74 ✓	89 ✓	[6], [74]–[84]
Salicylates:	0.82 (0.75-0.90)	(*N* = 6, *n* = 112 000)	[59]	74-73 ✓			74 ✓		[74], [75], [84], [85]
Indirect thrombin inhibitors:	0.91 (0.84-0.98)	(*N* = 6, *n* = 31 402)	[64]	74-73 ✓			74 ✓		[75], [84]
Direct thrombin inhibitors:	0.76 (0.59-0.98)	(*n* = 1 883)	[65]	74-73 ✓					[74], [84]
ACE inhibitors:	0.79 (0.71-0.88)	(*N* = 8, *n* = 38 315)	[66]	89-73 ✓				89 ✓	[84], [86], [87]
Angiotensin-renin inhibitors:	0.92 (0.87-0.97)	(*N* = 26, *n* = 108 212)	[67]					50 ✓	[88]
β-blockers:	0.69 (0.59-0.82)	(*N* = 9, *n* = 12 825)	[68]					89 ✓	[75], [84], [87], [89]
Calcium channel blockers:	0.83 (0.67-1.03)	(*N* = 28, *n* = 179 122)	[66]					89 ✓	[75], [84], [87], [89]
Diuretics:	0.79 (0.69-0.92)	(*N* = 42, *n* = 192 478)	[69]					89 ✓	[84], [90], [91]
Antidepressants:	0.48 (0.44-0.52)	(*n* =93 653)	[70]	94-73 **?**	44-72-12-32 **?**	44-72 **?**	44-71 ✓	44-70-89 **?**	[51], [52], [92]–[99]
Anxiolytics:	N/A	N/A	N/A	27-47-72-73 **?**	27-48-12-32 **?**	27-47-72 **?**	27-47-71 **?**	27-47-70-89 **?**	[84]
Biguanides:	0.74 (0.62-0.89)	(*N* = 40, *n* = 29 734)	[71]	14-49-73 **?**	14-12-32 **?**	14-55 **?**	14-55 **?**	14-54-89 **?**	[75], [100]–[103]
α-glucosidase inhibitors:	0.36 (0.16-0.80)	(N = 7, *n* = 2 180)	[72]			17-55 **?**	17-55 **?**		[104]
Ethanol:	0.71 (0.66-0.77)	(N = 31, *n* = 504 651)	[73]	101-72-73 **?**	12-32 **?**	101-72 **?**	101-71 **?**	101-29-50 **?**	[86], [105]–[108]

ACE denotes angiotensin-converting-enzyme;? indicates "proposed"; ✓ indicates "in use". Drug class and salient examples are given as follows: *Statins:* atorvastatin (Lipitor); *Salicylates*: Aspirin; *Indirect thrombin inhibitors:* glycosaminoglycan (Heparin); *Direct thrombin inhibitors:* Bivalirudin (Angiomax); *ACE inhibitors*: lisinopril (Prinivil); *Angiotensin-renin inhibitors*: Aliskiren (Tekurna); *β-blockers*: propanolol (Inderal); *Calcium channel blockers*: benzothiazepines (Diltiazem); *Diuretics*: thiazides (Indapamide); *Antidepressants*: selective serotonin uptake inhibitors (Sertraline); *Anxiolytics*: benzodiazepines (Alprazolam); *Biguanides*: metformin (Glucophage); *α-glucosidase inhibitors*: acarbose (Precose).

An increase in the number of possibilities generates future research and development opportunities [109]. New combinations of drug classes allow the possibility of creating a polypill or fixed dose combination (FDC) that could be used to decrease the risk of CHD [6], [8], [109], [110]. The economic impact of such a development would aid the developing world in combatting CHD [8], [21], [25], [58], [111]–[113].

The economic feasibility of the polypill stems forth from the adherence and combined effect of the drugs [113]. Establishing the impact of a polypill requires the analysis of each individual drug. Cost-effectiveness studies are performed for each new drug that enters the market [114], [115]. However, comparisons of the different drug classes are not routinely performed due to the fact that several companies that would need to be involved [62]. This study aims to provide a comparison between the economic impacts of the different drug classes.

1.4 Economic influence of coronary heart disease intervention

Determining the economic impact of an intervention can be done through several different methods. These methods allow the stakeholders to quantify how economically feasible their product is and can be used to compare different options with each other [115]. Comparison between the different analysis techniques that are used gives an indication of what method would be suitable to use within this study.

1.4.1 Economic analysis techniques

The branch of economics that describes pharmaceutical products and strategies is pharmacoeconomics. It uses techniques such as cost-benefit, cost-effectiveness, cost-minimisation, cost-of-illness and cost-utility analyses in the pharmaceutical industry [115]. Comparisons between different products or strategies are made, resulting in recommendations. The applicable analysis is determined by the desired outcome and the purpose of the study [116].

Pharmacoeconomics combines economic as well as humanistic components [117]. The humanistic components most commonly include: quality of life, patient preferences and satisfaction [115]. The humanistic components relate the economic results to a standardised reference that indicates acceptance by the population [118]. Different combinations of economic and humanistic components yield different results. It is therefore important that the combination must be identified correctly.

In 1998 the World Health Organization (WHO) developed the CHOICE (CHOosing Interventions that are Cost-Effective) project [62], [119]. The objective of this project was to develop a standardised method for establishing the cost-effectiveness of interventions.

Further objectives include the compilation of databases and country contextualisation tools. Following this methodology, as shown in Figure 4, enables result interpretation and recommendations on the cost-effectiveness of the interventions for CHD [118].

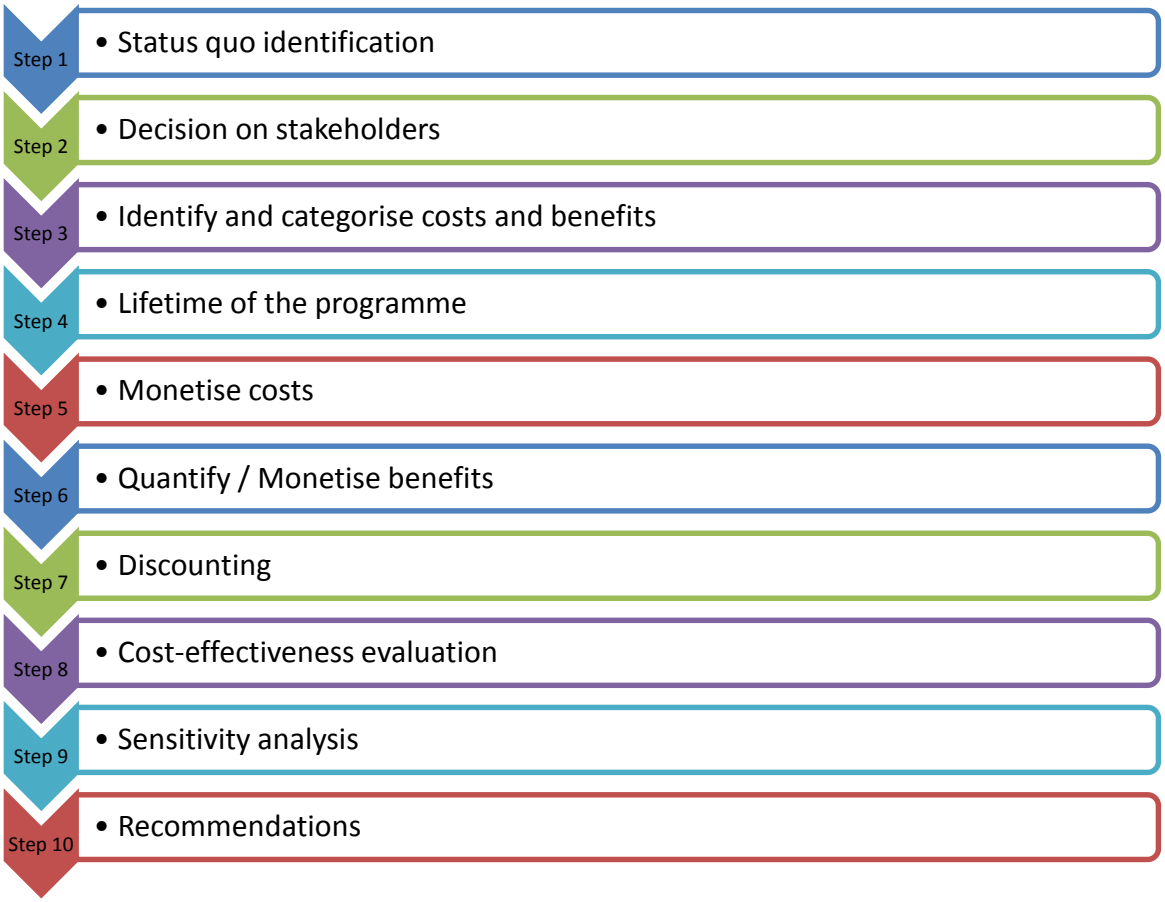


Figure 4: WHO-CHOICE steps for conducting a cost-effectiveness analysis

The process of conducting a cost-effective analysis as prescribed by the WHO-CHOICE project is shown in Figure 4 [62]. It consist of ten main steps that should be followed to give a complete representation of the process. Each individual step will be explained below and the applicability or assumptions that are used in this study will be stated.

Step 1: Status quo identification.

Identifying the status quo is the first step of completing an analysis. The status quo is the baseline situation without the programme or policy. During this step the influence of the product or strategy being analysed is excluded to obtain a reference point for the study. It is also during this step that the type and period of the analysis should be chosen. The type of analysis depends on the required outcome, while the period can be either pre-, post- or during implementation of the strategy.

In this study the status quo and reference, for the cost-effectiveness analysis (CEA), will be a model simulation without any interventions. CEA focuses on multiple interventions and is used most frequently throughout similar studies [3], [58], [62], [113], [120]–[127]. Cost-benefit analysis (CBA) was considered as an additional type, but this focuses on single programmes or variations within the programme. Comparing costs and interventions of different types is more adequately described by CEA and is therefore the chosen method [62], [118], [128], [129].

The purpose of the analysis is to predict what intervention would be most beneficial, as well as cost effective. All steps will be performed before the intervention is prescribed and followed. Results from the analysis will serve as predictions on outcomes that would be achieved after implementation.

Step 2: Decision on stakeholders.

Stakeholders for the analysis can range from public or private funding schemes to an individual. Deciding on whose point of view the study will represent plays a major role in the study design cost [130]. Boundaries for the costs and benefits are determined by the stakeholders, since they determine the domain of the assessed parameters [129].

Narrow boundary levels reduce the number of costs and benefits that should be assessed. Such boundaries result in the possibility of excluding important variables which spill over to other jurisdictions. It is important to identify such variables even if they are not quantified within the specific study. Focussing on the most common costs and benefits within a jurisdiction reduces the probability of missing such parameters [119].

Focus during this study will be placed on the individual and the applicable expenditures and benefits. The individual will follow an intervention and is assumed to pay for it by him or herself. Costs and benefits, such as medical aid or state funding, are excluded from this study even though this would alter the final intervention choice, thus excluding the influences that external funding would have on the outcomes.

Step 3: Identify and categorise costs and benefits.

Identifying and categorising the costs and benefits further defines the boundaries of the study. All inputs into the analysis that would impact the outcome negatively is defined as costs. Benefits are defined as the positive effects received into the system [62]. Both these effects can be classified within several categories. The common category descriptions used are: real or transit, direct or indirect, tangible or intangible, and financial or social [129].

For this study the benefits and costs will be limited to the interventions as identified in the integrative model in Figure 3. The interventions will also be kept separate and not combined in this analysis. This allows the categorisation of both the costs and benefits to be done according to the stated groupings.

Benefits and costs are classified as real, direct, tangible and financial parameters. They are deemed real since the effect that it has on the system represents a net gain or loss. Resource distribution is not altered or redistributed into or out of the outside boundaries as would be the case with transit factors [129]. The classification of direct stems from the close relatedness to the primary objective of the study. No additional costs or benefits are spilled over into the system since adverse effects of the interventions are excluded in the study.

Specific adverse effects and the related costs are excluded from the design of the study. Each intervention has adverse effects associated with it. Probabilities of experiencing an adverse effect vary for each individual and would require future research [29]. Compensation for negative effects are added to the quality adjustment parameters of each model state. It is assumed that prevalence and invasiveness of each adverse effect is similar for all interventions [131]. Adverse effects therefore influence the outcome of the study but not explicitly differently for each intervention.

Both the benefits and costs are tangibly and financially related to the individual. Expenditure made on interventions and the decreased relative risk for CHD impacts the individual directly. Cultural and societal impacts are not considered in the study, since it is performed from an individual's perception. The prescribed intervention is not related to the societal benefit and is therefore excluded in this personalised study.

Step 4: Lifetime of the programme

The programme time frame is dependent on the desired outcomes. Lifetimes of predictive studies are dependent on the termination period. The termination period is defined by the time the final outcome is to be evaluated. All individuals are assumed to have died at this stage of the study. They will have followed an intervention since entry into the programme and stop at death.

No changes are made to the analysis prior to the termination thereof. Therefore the reassessment of structures is not necessary. Parameters will change within a single simulation based on the inflation or deflation of the periods. However, the base values of the parameters will remain the same throughout the study.

Step 5: Monetise costs.

Financial values and homogeneity are added to the costs through monetisation. Variables having a negative impact are monetised to create a uniformity for comparison in the values. Costs in this study are monetary throughout and no conversion to a fiscal value is required. Capital costs, sunk costs and indirect costs are not applicable in this study, due to the individualistic perspective and the boundary placed on external funding.

Step 6: Quantify / Monetise benefits.

As with the costs, the benefits should be converted to comparable units. Monetisation of the benefits is not necessarily required, since the outcome is based on cost per benefit ratio. Quantification of the benefits are done in this study through the number quality adjusted life years (QALY) [129]. The QALY added in comparison with the status quo, is the outcome benefit being analysed. Relative risk reduction increases the QALY and is therefore incorporated into analysis through this. Other benefits are excluded and no further conversion is needed.

Step 7: Discounting.

The power of money changes over time and is also different for every country. Predicting the true power at the end of a period can also not be done. Costs and benefits are therefore discounted to obtain the value as it would have been at the beginning of the study. This allows comparison to other values at the same point in time. This describes the net present value (NPV) of the outcome at the current point in time [61], [132], [133].

Comparison between studies in different countries cannot be done unless one or both of the values are converted to similar units. There are several options available to do this, such as converting the costs to a uniform currency. The uniform currency frequently used in CEA is international dollars [62], [121], [134], [135]. Using the purchasing power parities (PPP) of the countries, the values are converted to international dollar and can be compared [23], [121], [133], [136].

Costs and benefits are discounted annually in this study to obtain the NPV for each predicted year. Discount rates are similar to those used in similar studies and as recommended by the WHO-CHOICE guidelines. All costs are converted into international dollars according to the necessary PPP values. South African GDP inflation will be used to adjust it to 2013/2014 values. These costs and benefits can now be used in the cost-effectiveness evaluation.

Step 8: Cost-effectiveness evaluation.

Weighing the costs and benefits up against each other determines what the ratio between the two is. This is done for all components that are evaluated to make recommendations on each. Calculating the cost per benefit ratio is the basic indicator used to make decisions [136]. Ratios, such as incremental cost-effectiveness ratios (ICER) can be used for indicator comparison [115].

Cost per benefit and ICER will be applied within this study, as within other studies [13], [113], [123]–[126], [135], [137]–[139]. General indicators will provide the results for the individual interventions. Interventions will be compared to each other by using ICER to determine the feasibility over one another. Having comparative results enable prescribers to make more informed choices when recommending an intervention.

Step 9: Sensitivity analysis.

Each variable used throughout the evaluation influences the final outcome in different ways. It is necessary to determine the magnitude of the effect of each to prevent skewing of results [62], [118], [140]. This is done by conducting a sensitivity analysis on the variables. A probabilistic sensitivity analysis [56], [58], [124], [125], [132], [141]–[143] and Monte Carlo simulations [8], [123]–[125], [136], [142] are the most frequently used methods for this purpose.

Monte Carlo simulations and a multivariable probabilistic sensitivity analysis will be performed. This will be used to verify the results and establish the effect of each variable on the system. Conclusions can be drawn on what impact a change to a variable would have on the outcome. This will aid in compiling the final list of recommended interventions for the individual.

Step 10: Recommendations

The final results should be interpreted after the previous process has been completed. Evaluating all the results as a whole, generates a holistic view and proper recommendations can be made. The final recommendations within this study will be a list of possible interventions that an individual can follow for a reduced CHD relative risk.

Generating a list of recommendations requires a predictive model capable of performing the aforementioned steps. Such model should be able to simulate the survivability of an individual, as well as the economic impact of interventions and other factors. Several modelling techniques have the required capabilities but have restrictions that limits their usefulness

[115], [144], [145]. Choosing the appropriate technique will allow a highly predictive survival and economic model.

1.4.2 Analytical modelling techniques used in economic evaluation

Analytical modelling techniques are used in many fields to predict outcomes and simulate scenarios [144]. Some techniques applied in economic evaluations for healthcare are decision trees and Markov models [62], [141] along with discrete event simulation [146] and mathematical modelling [144]. The simplest technique is decision trees but this is restricted due to several constraints [146]. Markov models use the same logic as decision trees by using a transition matrix to make decisions and are used more frequently [143] .

Decision trees give a layout of the possible routes that could be followed in an expanded manner. A hypothetical decision tree for CHD is given in Figure 5. At a specified stage a decision is made on what branch the simulation follows. The decision is based on the available routes and the probability of the branch being followed [147]. During each stage the available branches are specified since the model is unable to move back to a previous decision point [147].

Expanding the number of branches and decision nodes for each stage increases the complexity of the model. The number of routes increase exponentially for simulations with a long time horizon and multiple health states [143]. Analysing such a complex model is difficult and other recursive modelling techniques are more favourable. Decision trees are favoured in simulations with limited model nodes and simulation stages [143], [147].

A further restriction with this technique is that it does not state when an event occurs [147]. This restriction can be overcome by using probabilities to determine the distribution after every stage. However, each stage represents one simulation cycle and therefore increases with long time horizons with small intervals [143]. An expansive model is therefore needed but restricted by the abovementioned increased complexity.

The decision tree in Figure 5 [125] shows how the technique can be applied to CHD. A healthy individual can either stay healthy, experience a CHD event or die of natural causes. If the first option (healthy) is chosen, the individual will have the same routes available for the second decision. Death is a termination state and no further options are available if an individual enters it. Similar to the decision to remain healthy, the choice of a CHD event is also a continuous route.

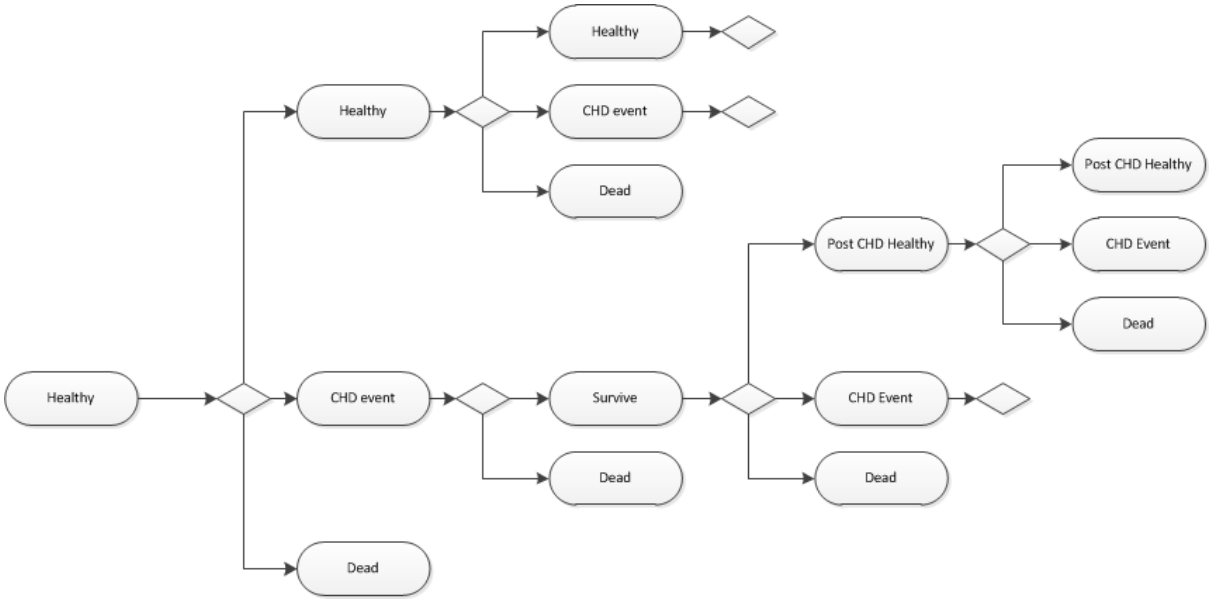


Figure 5: Hypothetical decision tree for CHD Adapted from "Cost-Effectiveness of Aspirin treatment in the primary prevention of cardiovascular diseases in subgroups based on age, gender, and varying cardiovascular risk." by Greving *et al*. [125]

The individual will either die from the event or survive it and continue along other routes. Secondary CHD events are possible if the initial one was survived, but being healthy afterwards is also likely. Being in either a *post-CHD* healthy state or CHD event will cause the simulation to continue in a similar manner until the individual ends in the death state. From this application it is seen that the complexity increases with an extended timeframe. A simplified approach is required to simulate multiple health states over a long period of time.

Markov models are used to simulate recursive processes and complex systems [143]. Markov models have been used in healthcare evaluations as early as 1983 [147]. Several guidelines have been published to help develop a suitable model for the desired application [62], [143], [146], [147]. Combining these guidelines with similar published studies gives a basis for assembling a health model. Economic evaluation studies for CHD and cost-effectiveness of pharmaceutical interventions mainly use Markov models [13], [29], [56], [58], [61], [62], [111], [113], [120], [125], [132], [137]–[139], [142], [146], [148]–[154].

Several layers of detail can be added to these models [144]. Basic layers such as healthy, CHD and death can be the only levels within the model. Other models can include several different CVDs, other causes of death and adverse effects of interventions [29]. Figure 6 shows the Markov model for with the same design as in Figure 5. This is a simplified model that focusses on four main states with pathways similar to those in the decision tree model.

Individuals in the healthy state can either stay healthy, die of natural causes, or experience a CHD event. Experiencing a CHD event leads to either death from the experience or to a post-event healthy state. An individual has the opportunity to stay in the *post-CHD* healthy state until he or she dies of natural causes. However an additional CHD event can be experienced and would cause the model to be reiterated from the CHD event state. Death is the termination state and all individuals will remain inside it once they have moved into it.

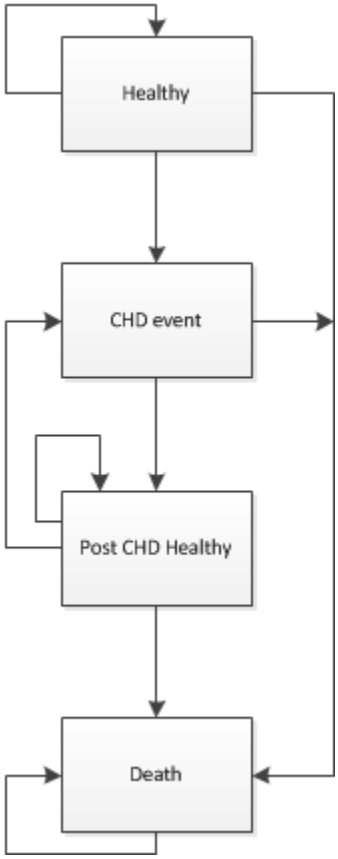


Figure 6: Hypothetical Markov model of CHD events

These states form the basis of Markov models for CHD studies. Changes to the base design are dependent on the application and study requirements. Interventions are not added as separate states to the model, but rather as variables to the transition probabilities [145]. Moving from one state to another is determined by an *n x n* transition matrix [143]. Each pathway has a probability assigned to it. At the end of each time cycle the distribution within each state is determined by these probabilities [146].

Having the distribution between the states enables the researcher to calculate costs for the current cycle. A cost variable is defined for each state and applied during each simulation cycle [146]. Total cost for the simulation can be determined from the individual cycle values. The total costs can be compared to a baseline value to determine if it is more or less costly

[115]. Costs and benefits from the study are combined to establish the net effect of the study at the end of the simulation [146].

The benefits for the study are not defined directly at the end of the decision tree or Markov simulations. Benefits are calculated from the population distribution for each cycle, similar to costs. Each state is adjusted with a quality related to the living standards for the particular situation. Years that the population is treated as alive are calculated for the distribution and adjusted with the quality variables. Quality adjusted life years (QALY) is comparable to that of the baseline and would yield the benefit for the study. [62], [143], [145], [146]

Results obtained for the benefits and costs for the study can be used for comparing different studies [118]. Studies commonly focus on a single comparison between similar or an alternative programmes [115]. This study compares alternative pharmaceutical programmes for the prevention of CHD. Comparison between several alternatives for CHD has previously been done [57], [89], [111]. However these focussed on two or three drug classes or lifestyle modifications reducing the relative risk of CHD.

In this study 13 drug classes are evaluated for their cost-effectiveness toward CHD risk reduction. It is based on a similar study comparing five different drug classes [58]. Aiming to derive a method and obtain results for person-specific cost-effective interventions.

1.5 Aims of the study

This study aims to ultimately provide a list of possible cost-effective coronary heart disease (CHD) interventions specifically tailored for an individual, indenting to aid the normal individual as well as a medical professional in deciding between available interventions. Results are not intended to replace the opinion of a medical specialist, but rather provide additional diagnostics and preventative measures.

A person-specific risk profile will be derived by using serum biomarkers and the related relative CHD risk factor. By using the profile, intervention altering high risk biomarkers can be identified as possible treatment routes. CHD relative risk values for the intervention are incorporated in a survival model to determine the benefits of each respectively.

The simulation model is used to provide a probabilistic distribution between predefined CHD-related health states. Survivability, benefits and costs can be obtained for comparability between the possible interventions. Interventions with high benefits and low costs will be favoured since the net positive effect will be larger. Compared results are used to generate a list of CHD-related interventions, quantifying the cost-effectiveness of each.

1.6 Scope of the study

Cardiovascular medicine, and management of other diseases related to the circulatory system, is a broad field with several different sub-divisions. In this study focus will be placed on coronary heart disease (CHD) and related risk reducing interventions. The study will be done from a patient perspective to establish the patient-specific effects. These effects include life year changes as well as costs related to the routes followed.

This study uses an integrative model to determine what serum biomarkers affects the relative risk for CHD. From the model, biomarkers are identified and their respective relative risk for CHD is quantified. Pharmaceutical interventions that influence the biomarkers and CHD hallmarks are deduced from the model and literature. Economic cost-effectiveness evaluations are performed on the interventions.

Economic evaluation of the interventions is based on the guidelines provided by the World Health Organization's CHOosing Interventions that are Cost-Effective (WHO-CHOICE) programme. The following general assumptions are made with respect to the guidelines:

- A status quo will be analysed as reference point for intervention comparison. No interventions will be applied to the status quo.
- Cost-effectiveness analysis will be performed to determine the economic impact of the interventions.
- A Markov model will be used to simulate the survivability of the population analysed.
- Interventions for the study are limited to pharmaceutical interventions as identified from the integrative model. Interventions, such as the health factors, are not included in the study.
- Interventions are analysed separately and not combined in any manner.
- The programme lifetime is deemed to start at the age of the individual and will continue to a maximum age of 105 years.
- Costs will be monetised for each health state within the model. Costs of interventions will be added to the respective states adjusting the state cost.
- Benefits will be quantified by quality adjusted life years.
- Monetary values are converted to international dollars by using purchasing power parities of the respective countries.
- All monetary values are adjusted to represent 2013/2014 values by using South African GDP inflation.
- Costs and benefits are discounted annually.

- Cost per benefit and incremental cost-effectiveness ratios will be used as indicators for final results.
- Monte Carlo simulations and a probabilistic sensitivity analysis will be used for verification of the outcome results.

Economic evaluation as stated above will be performed on a distribution obtained from a survival model. A Markov model will be used in this study with four main health states. Interventions are not included as main modelling states within the layout. Interventions are included in the model by altering the transition matrix during each cycle. Costs related to adverse effects are excluded from the design, but enclosed within intervention variables. Interventions analysed are compared and a list is generated based on the net positive effect thereof.

Two case studies will be used to complete the analysis. Biomarkers and interventions are restricted to those identified for the relative case studies. The list will ultimately serve as a guide to possible interventions and is not intended to replace medical specialist opinion. The guide will provide a cost-effectiveness of CHD pharmaceutical interventions for a specific relative risk profile.

CHAPTER 2 – METHODOLOGY

2 Methodology

2.1 Biomarker analysis

As possible indicators of the presence of severity of CHD, the biomarkers of a patient should be measured and analysed. The combination of biomarkers for each individual are different and would require different prevention or treatment interventions. Real-time variation of biomarkers eliminates the need for real-time intervention modification. Biomarkers are measured through blood serum tests.

Blood tests are performed at most clinics and hospitals at the request of a patient or upon referral from a medical practitioner. The serum is analysed and indications are given of what biomarkers represent a high risk. High risk indicators are used to identify possible interventions to improve the respective biomarkers. In this study biomarkers are analysed based on the normal levels of each indicator.

A list is compiled of biomarkers with a significant influence on the risk for CHD for the patient. It is important that the list of identified biomarkers reflects the relevant biomarkers. This ensures that the best intervention or combination is prescribed. Biomarkers are arranged according to the relative risks that they hold for the patient. The biomarker with the highest relative risk will be listed first. The remaining biomarkers will be placed in a descending order until all those identified have been listed.

The acceptable limits of the CHD related biomarkers are indicated in Table 3. Serum test values are analysed and evaluated against the acceptable healthy limits. The results give an indication of which of the biomarkers are not within the acceptable healthy range. After comparison, high risk biomarkers are identified and listed to be used as input for the following process in the study.

Listed biomarkers reflect the risk of a patient in a simplified manner. Blood serum test values and results can be confusing and important risk factors could be missed. From the list a medical professional, as well as the patient, can easily identify which biomarker holds the highest risk and react accordingly.

Interventions related to the listed biomarkers can now be identified and prescribed. The interventions prescribed for the patient will be more specific for the risk factors of the individual. Generalised interventions that are unrelated to the individual's high risk biomarkers can thus be avoided.

Table 3: Normal blood values for salient serum biomarkers

Biomarker (class and salient examples)		Healthy reference range	Unit	Ref.
Coagulation marker:				
Fibrinogen		200 – 400	mg/dl	[155]
Inflammation markers:				
hsCRP		< 3	mg/l	[156], [157]
IL-6		< 8.9	pg/ml	[158]
TNF-α		< 15.6	pg/ml	[158], [159]
GDF-15		< 1200	ng/l	[160]
OPG		< 0.2	ng/ml	[161]
Lipid-related markers:				
Triglycerides		0 - 1.7	mmol/l	[162], [163]
LDL		0 - 3.4	mmol/l	[164]
HDL		> 1	mmol/l	[164]
ApoB		30 - 130	mg/dl	[165]
Leptin	Male	1.2 – 9.5	ng/ml	[166]
	Female	4.5 - 25	ng/ml	[166]
Marker of oxidative stress:				
MPO		< 600	pmol/l	[167]
Marker of vascular function and neurohormonal activity:				
BNP		< 100	pg/ml	[168]
Homocysteine		<15	µmol/l	[169]
Metabolic markers:				
HbA_{1c}		< 6	%	[170]
IGF-1	Male	50 – 182	ng/ml	[171]
	Female	56 - 179	ng/ml	[171]
Adiponectin	BMI < 25 Male	4 - 26	µg/ml	[159]
	BMI < 25 Female	5 – 37	µg/ml	[159]
	BMI 25 – 30 Male	4 – 20	µg/ml	[159]
	BMI 25 – 30 Female	5 – 28	µg/ml	[159]
	BMI >30 Male	2 – 20	µg/ml	[159]
	BMI > 30 Female	4 – 22	µg/ml	[159]
Cortisol		5 - 25	µg/dl	[172]
Insulin resistance (HOMA)		0.08 – 2.5	units	[173]
Necrosis marker:				
Troponins		< 0.1	ng/ml	[174]
Renal function marker:				
Urinary ACR		< 3	mg/mmol	[175]

HDL denotes high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin–to-creatinine ratio; GDF-15, growth-differentiation factor-15; LDL, low-density lipoprotein; HbA1c, glycosylated haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; RANKL or OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostasis model assessment; BMI, body mass index

2.2 Intervention identification

It has been found that generalised strategies are less effective in comparison to specific targeted interventions [5]. To increase the efficiency of an intervention the biomarker that should be treated must be known. Interventions can therefore be prescribed allowing the patient to follow more optimal strategies for his/her CHD risk. Individual interventions will contribute to the alteration of several biomarker values, stressing the need to compile a list of the least number of interventions with the greatest effect.

The ability of an intervention to affect the identified biomarker was deduced from the integrative model in Figure 3 and pathway information in Table 2. The pathway information was used to identify interventions affecting a specific biomarker. For example, anxiolytics inhibit cortisol via pathway 27 in Figure 3. This procedure was applied to all the drugs and the results are indicated (✓) in Table 4.

Summarising the interventions, as well as the health factors, which have an effect on each biomarker, Table 4 can be simplified and visualised in a new way, as shown in Figure 7. A simplified visualisation of myeloperoxidase (MPO) is shown in Figure 8. All elements are linked to coronary heart disease (red) as this is the focus point of the system. Biomarkers (green) are displayed with an increase in relative risk in a clockwise manner. Health factors (purple) and pharmaceutical interventions (blue) are displayed in a similar manner.

By using the diagram and visualisation, the list of interventions are added to the list of biomarkers that were identified. Interventions are arranged according to the relative risk for the patient. The intervention with the lowest relative risk is listed first. The remaining biomarkers are placed in an ascending order until all those identified have been listed.

This list identifies which interventions will be beneficial for the patient's condition. With the risks and possible interventions known, a survival model can be developed for the patient. The model quantifies the impact of the interventions and biomarkers. The costs for the intervention can furthermore be quantified from the survival probability of the individual.

Table 4: Influence of pharmaceutical drugs on biomarkers for CHD

Biomarker (class and salient examples)	Interventions													
	Statins	Salicylates	Indirect thrombin inhibitors	Direct thrombin inhibitors	ACE inhibitors	Angiotensin renin inhibitors	β-blockers	Calcium channel blockers	Diuretics	Antidepressants	Anxiolytics	Biguanides	α-glucosidase inhibitors	Ethanol
Lipid-related markers:														
Triglycerides	✓									✓	✓	✓		
LDL	✓									✓	✓	✓		✓
HDL	✓									✓	✓	✓		✓
ApoB	✓									✓				
Leptin	✓	✓				✓	✓	✓		✓	✓			✓
Inflammation markers:														
hsCRP	✓											✓		
IL-6	✓	✓								✓	✓	✓		
TNF-α	✓	✓								✓	✓	✓		✓
GDF-15	✓	✓								✓		✓		
OPG	✓	✓								✓		✓		
Marker of oxidative stress:														
MPO	✓	✓								✓		✓		
Marker of vascular function and neurohormonal activity:														
BNP						✓	✓	✓		✓	✓			
Homocysteine	✓									✓				
Coagulation marker:														
Fibrinogen	✓	✓	✓	✓						✓	✓			
Necrosis marker:														
Troponins	✓				✓	✓	✓	✓	✓		✓	✓		
Renal function marker:														
Urinary ACR	✓													
Metabolic markers:														
HbA_{1c}											✓	✓	✓	✓
IGF-1										✓		✓		✓
Adiponectin	✓									✓		✓		
Cortisol								✓			✓	✓		
Insulin resistance (HOMA)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

HDL denotes high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin–to-creatinine ratio; GDF-15, growth-differentiation factor-15; LDL, low-density lipoprotein; HbA1c, glycosylated haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; RANKL or OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostasis model assessment; ACE, angiotensin-converting-enzyme, ✓ indicates identified influence

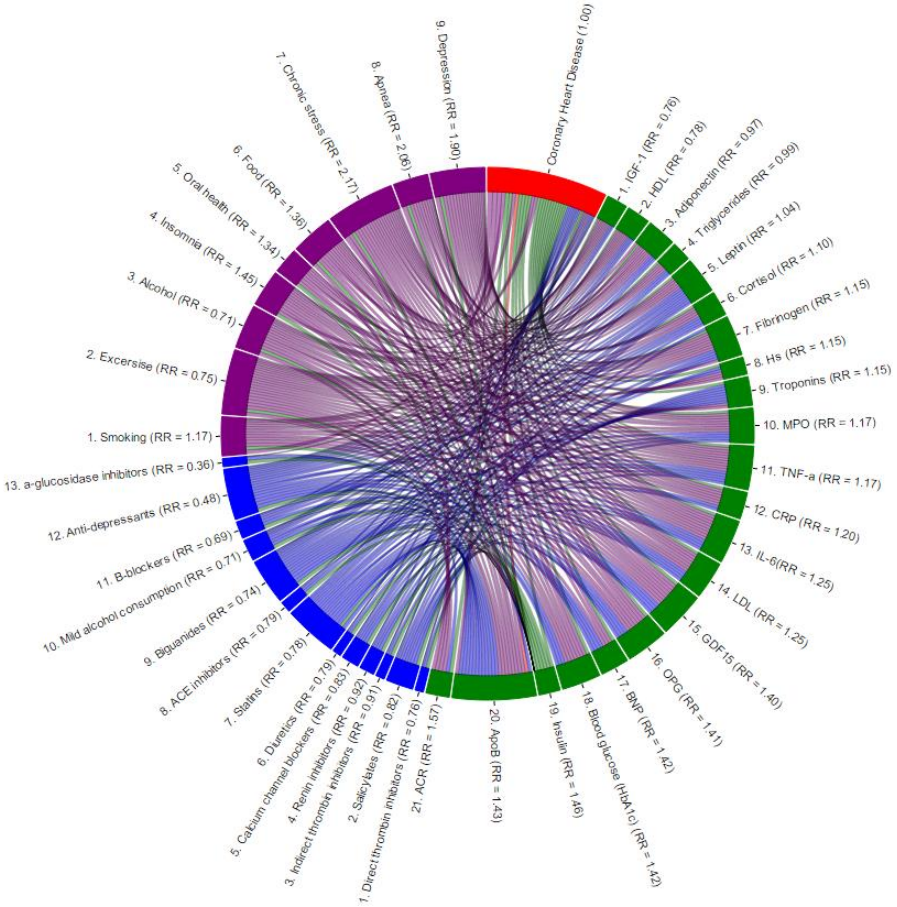


Figure 7: Visualisation of the influences that interventions have on biomarkers for CHD

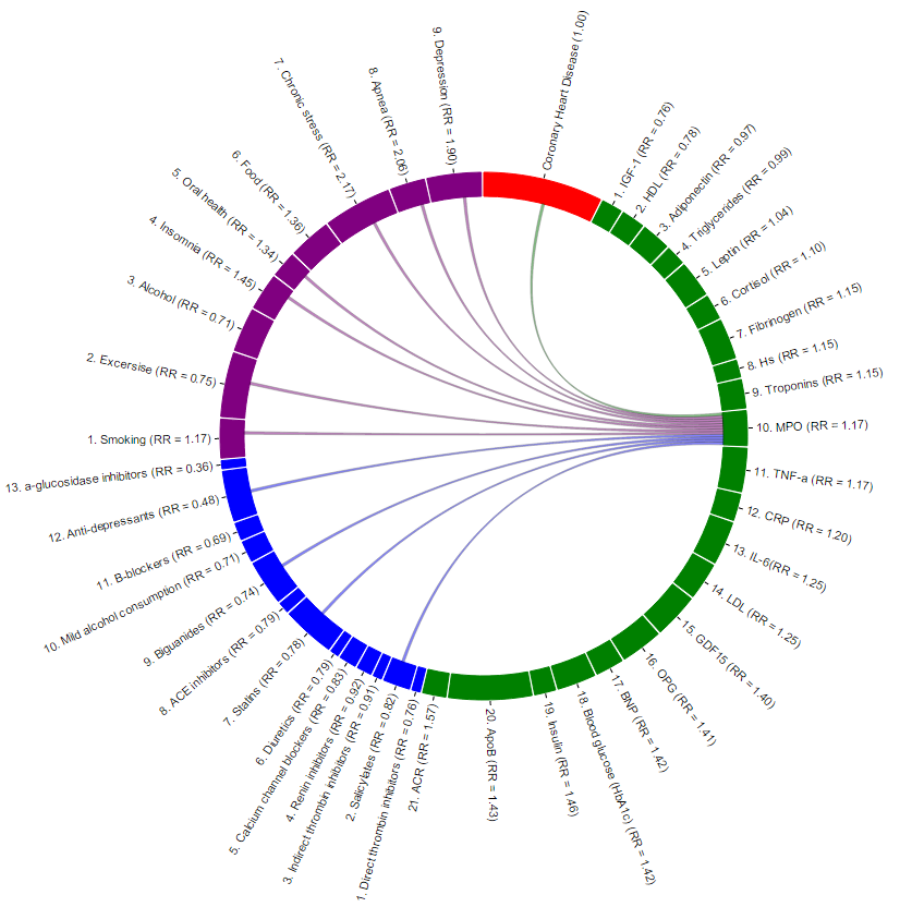


Figure 8: Visualisation of interventions that influence MPO

2.3 Survival simulation model

The survival probability of a patient depends on several other factors not defined by the biomarkers. These factors include variables such current age, risk of dying from non-CHD related causes, and the quality of living a year in a certain health state. The combination of these factors should be contained in the model, accounting for several different outcomes. These factors should be able to follow and contribute to the survival probability of the patient. In order to achieve these contributions, the model will allow a simulation to follow several paths to a single termination state.

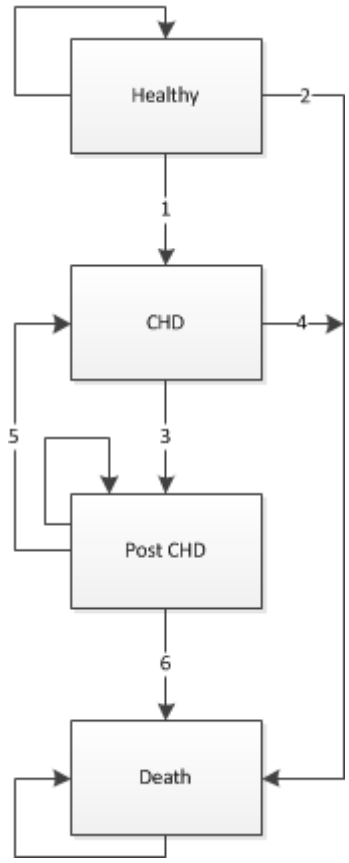


Figure 9: Markov survivability model outline for CHD

Markov modelling will be used to simulate the survival probability of a patient. Markov models use different states with transition pathways between states [145]. Using transition pathways the simulation will follow different pathways for each combination of variables. The model (Figure 9) consists of four states in which the patient can be classified. Each state represents a stage of life a person could be in.

From Figure 9, the four main states are: *healthy*, *CHD*, *post-CHD* and *death*. Each of these states have different properties allocated to them. In the *healthy* state, the patient is assumed to be asymptomatic for any CHD. By remaining asymptomatic throughout the simulation

lifetime the patient will die from causes unrelated to CHD. The patient is moved to the *CHD* state when a CHD event is experienced.

In the *CHD* state the patient has experienced some form of coronary heart disease event. CHD incidents are mostly a rapid event followed by treatment and close observation. The *CHD* state represents the cycle of treatment and observation following a CHD incident and the event itself. The patient will remain in the *CHD* state for a full simulation cycle. It is assumed that the patient will not experience another incident in the following cycle. Patient monitoring is sufficient to prevent another incident in the next simulation cycle [176]. All patients in the *CHD* state will therefore move to a downstream state in the next cycle.

From the *CHD* state the patient will enter either the *post-CHD* or the *death* state of the simulation. In the *post-CHD* state the patient is deemed asymptomatic for coronary diseases and follows the same life style as in the healthy state. The interventions and effectiveness thereof, will be the same as if the patient was in the *healthy* state. It is furthermore assumed that the relative risk of the patient remains the same for the *post-CHD* and *healthy* states.

However, transition probabilities for the patient in the *post-CHD* state will be altered due to the collateral damage caused by the CHD incident. Quality of life for patients in the *post-CHD* will be reduced due to the previously experienced event, excluding the intervention reduced quality adjustments. The probability of dying of natural causes will increase compared to the probability in the healthy state. Patients in the *post-CHD* state have a probability of experiencing an additional CHD incident.

A patient in the *post-CHD* state can experience a CHD incident similar to when in the *healthy* state. This is an additional incident, but is treated as if it was the initial incident. The probability of experiencing a CHD incident differs for the *post-CHD* and *healthy* states. All patients in the *post-CHD* state can experience several CHD incidents throughout the simulation. Additional CHD incidents are unrelated to the number of incidents following the initial incident. Additional CHD event probabilities remain the same, since each additional event is mutually exclusive.

The fourth and final state of the model is the *death* state. Patients in the *death* state are deemed dead. This serves as both the adsorption and termination state of the simulation. All patients entering the simulation will end in the *death* state after repeated cycles. It is impossible for a patient to leave the *death* state once it has been entered. No transition pathways leave this state, since it is the termination state.

Movement between the different states is done through temporary short term transition states. Each transition state connects two main states with each other. Each transition state has a

probability that patients in the main state will pass through it to the following state. At the end of each simulation cycle all transition states are empty. It is assumed that all patients that enter it has passed through to the applicable main state. A transition state does not connect to another transition state without passing through a main state.

It is possible for multiple transition states to leave or enter a single main state. All main states therefore have a different combination of transition states attached to it. Figures 10 – 13 are extracted from Figure 9 focussing on each main state and the transition states attached to it.

The *healthy* model state (Figure 10) is the only main state with no incoming transition states. All patients to be simulated are assumed to be already inside the *healthy* state at time 0. Additional patients cannot be added after the simulation has started. The population of patients inside the state is dependent on the simulation type to be followed and the variables to be used. It is further assumed that all individuals inside the *healthy* state will move to another state before the simulation is completed.

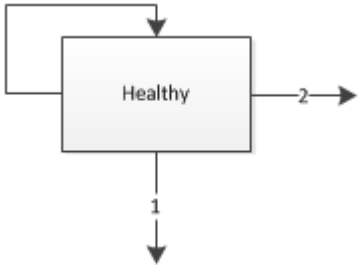


Figure 10: Healthy Markov state

Individuals in the simulation can leave the *healthy* state through one of two ways. Healthy individuals can move to the *CHD* state via transition pathway 1. Individuals passing through this transition state experience a CHD incident and enter the *CHD* state where all treatment and observations for the incident take place. This transition happens rapidly without any delay in the simulation. Another pathway leaving the *healthy* state goes to the *death* termination state.

Following the transition pathway from *healthy* to *death* directly, represents death by non-CHD related causes. Every person has the probability of dying of non-CHD causes during a simulation cycle. Transition pathway 2 represents the death by natural causes for individuals in the *healthy* state. Individuals following this pathway do not experience any CHD related incidents. Individuals that do not leave through either of the transition states will remain healthy and continue living with the same parameters applied to their survival probabilities.

During the simulation cycles several patients will pass from the *healthy* state to the *CHD* state (Figure 11). The *CHD* state has two main incoming and two outgoing transition states attached to it. All patients will leave the *CHD* state during the second cycle through one of the two outgoing transition states. Individuals who survive the *CHD* incident and the cycle in the CHD state will move to the *post-CHD* state (Transition state 3). Transition state 4 goes to the *death* state and the individual is deemed dead.

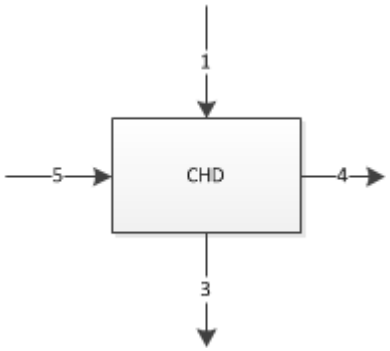


Figure 11: CHD Markov state

Transition to the *death* state from the *CHD* state occurs when an individual dies from a CHD incident or related causes. Two main criteria and probabilities are used to determine the number of individuals passing through to the death state. The first group is determined by the individuals passing away while experiencing the CHD event. Individuals passing away in the *CHD* state due to other causes will form the second group passing through to the *death* state.

Individuals who do not survive the incident will follow this pathway during the next simulation cycle. Individuals will first enter the *CHD* state for a full cycle before going to the *death* state. Entering the period for one cycle accounts for the costs and time associated with initial treatment of the incident experienced. Not all individuals die when experiencing an incident and are likely to receive treatment. The period in the *CHD* state accounts for the period to care for the patient and prevent him/her from dying.

The second group will die from non-CHD related cause after recovering from the CHD incident. All natural deaths from the *CHD* state are assumed to be aggravated by the experienced incident. Individuals can initially recover from the incident and survive it. Deaths by natural causes are included in the non-CHD related deaths passing through to the termination state. The total deaths leave the *CHD* state during the next simulation cycle via transition state 4. Surviving individuals move to the *post-CHD* state, while no one remains in the *CHD* state.

Individuals in the *post-CHD* state (Figure 12) survived a CHD incident and can continue through the simulation. They can follow similar transition states as those individuals in the *healthy* state. The *post-CHD* state has a single income from the *CHD* state and two outgoing

transition states. Individuals enter the state from the *CHD* state (transition state 3) and could go to the *CHD* and *death* states through transition states 5 and 6 respectively. It is possible to remain in the *post-CHD* state and continue living.

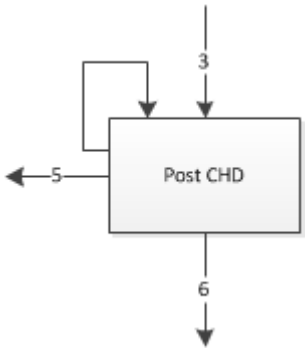


Figure 12: *Post-CHD* Markov state

The risk of experiencing a CHD event does not go away if a previous incident has been experienced. The risk associated with an additional CHD incident differs from that of an initial incident. Individuals could experience an additional CHD incident and move back to the *CHD* model state through transition state 5. All individuals can die of other causes as in the previous modelling states. The risk of dying of natural causes has been adjusted to account for secondary damages caused by the previous CHD incident/s.

Transition state 6 represents the natural death of individuals in the *post-CHD* state. This is also the final transition state for the model leading to the *death* model state (Figure 13). As the final state in the model, *death* has no outflowing transition states and absorbs the simulated individuals. A number of individuals will enter the *death* state during each simulation cycle and will be unable to leave it. All individuals entering the simulation will end in the *death* state if the simulation is continued indefinitely. With the use of this model different types of simulations can be conducted.

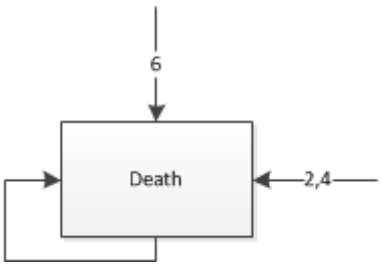


Figure 13: Death Markov state

This simulation can be conducted for a cohort or for a group of individuals with different variable values. Cohort simulations will be performed in this study, where the focus is on the results for an individual. Cohort simulations use a hypothetical group of, for example, 10 000

patients with similar variables and probabilities [115], [143]. It is therefore assumed that the parameters of the cohort are the same. By using the same model parameters, the individual patient will be able to follow up to 10 000 different routes through the simulation.

Simulation procedure

The cohort starts in the initial state as healthy individuals at time 0. During each simulation cycle the transition probabilities are applied altering the distribution of the cohort in each state. This can be repeated to build a profile of the number of patients in each state over time. The profile of each state can be used to determine the most plausible effects the intervention has on the cohort. The profile will also illustrate the possible survival curve for the cohort which can be used for additional recommendations.

Although, the focus of this study is on the individual, population simulations will also be done. The population simulation (Monte Carlo simulations) will be used to compare the results of an individual from the cohort, to that of a population with similar parameters and no interventions. In Monte Carlo simulations each individual is assigned a random combination of variables for the simulation. The individual passes through the simulation as a cohort and the result is recorded. This is repeated for the entire population.

Several statistical analyses are performed on the population data. The mean, median, standard deviation and minimum and maximum values are calculated. Results from the individual simulation are compared to that of a random population to compare the individual to a large pool of information. Comparison between the data indicates if the response to the intervention is normal.

These simulations will additionally indicate the cost effectiveness of interventions for a specific patient. The simulation is performed using a base case as reference point. This status quo is used to identify the net effect of the interventions when simulated.

The simulation procedure is described in Sections 2.4 – 2.6. Sections 2.4 and 2.5 describe the simulation for the status quo and interventions respectively. While the cost-effective analysis is described in Section 2.6. Section 2.7 describes the method for conducting the sensitivity analysis. Seeding, assumptions and calculations related to each variable is described in detail throughout these sections.

2.4 Status quo parameters and assumptions

The effectiveness of interventions is quantified by comparing it to a baseline. The baseline represents the life of an individual without the influence of any interventions. Parameters influencing the status quo determine the basic survival curve for the simulation and each state. By using the basic curve as a reference point the positive or negative effect of the intervention can be identified and quantified.

The basic curve will contain all main model variables except for those related to the interventions. Variables used throughout the simulation in the status quo are summarised in Table 5. The variables determine the distribution and transition between the states, and include adjustments done to compensate for the non-ideal simulation reality.

The main variables determining the duration of the simulation are the *size* and *cycle length* variables. Adjusting the size of the hypothetical cohort will vary the number of times an individual is run through the simulation. As the transition probabilities of the states remain constant, the size of the cohort will only determine the scale of the simulation [143], [145], [147]. The cohort is distributed percentage wise and should therefore be chosen to represent an individual and not a fraction of an individual as far as possible.

A large cohort will give a better representation of individuals, compared to a small cohort. For this study the cohort was chosen as 10 000. This will scale the distribution 100 times in order to represent complete individuals and not fractions. The distribution will not change but all values will represent 100 times more individuals. The final outcome of the simulation will be influenced by the *cycle length* variable, unlike the size of the cohort.

The cycle length is the time it takes to complete one simulation cycle. The cycle length can be days, weeks, months, years or several years. It is therefore important to get a cycle length that gives a good representation of the risks being simulated. CHD events occur instantaneously and are mostly unpredictable as to when they will happen. Even though the event occurs rapidly, the cause, effect and treatment takes place over a longer time.

Infectious diseases have a short term impact and can rapidly spread through a population. Incubation periods, infectious transfers and symptom development happens mostly within a week or a month. This will cause the simulation cycle length to be days, weeks or mostly months [143]. When compared to CHD events this cycle length will be relatively short and would not represent the development of such an event.

Table 5: Status quo model variables

Variable name	Value	Description	References
Size	10 000	Size of the hypothetical cohort being simulated.	[123], [131], [134], [138]
Cycle length	1 year	Length of one simulation cycle.	[13], [139], [142], [143], [149], [152]
Age	45 (case study 1) 55 (case study 2)	Initial age of the individual being analysed.	
oDR	3%	Discount rate for outcomes.	[58], [120], [127], [132], [154]
nDeath35 **nDeath45** **nDeath55** **nDeath65** **nDeath75** **nDeath85**	0.061319 0.072708 0.115563 0.229347 0.393716 0.595133	Non-CHD related death risk for individuals over a specified age group. (35-44; 45-54; 55-64; 65-74; 75-84; 85+).	2013 South Africa standard life tables, [177]
pCHD	0.1	Probability of experiencing a CHD event in one simulation cycle.	[13]–[15], [59], [178]
pDCHD	0.11156	Probability of dying from a CHD event in one simulation cycle.	[13], [59], [176], [179]
pACHD	0.02883	Probability of experiencing an additional CHD event after experiencing a previous event.	[13], [152], [153], [176], [180]
PRR	1.13 (case study 1) 1.17 (case study 2)	Relative risk of the individual adjusted according to the identified biomarkers.	
qHealthy	0.97	Quality of life in the Healthy model state.	[132], [138]
qCHD	0.8	Quality of life in CHD model state	[13], [124], [125], [132], [138]
qPCHD	0.85	Quality of life in the *Post-CHD* model state.	[13], [132]

Risks associated with CHD events are normally categorised as a 1-year, 10-year, or 30-year risk [4]. By comparing the time associated with CHD events and infectious deceases, it can therefore be concluded that a longer cycle length should be used. When comparing the time frames reflected for the CHD risks the cycle length should be in annual periods. These periods could be a single year or over the course of several years.

The 10-year CHD risk gives an indication that a ten year cycle length could be used in the simulation. According to the World Bank [181], the average life expectancy at birth throughout the world is 70.8 years, with the highest at 83.8 years in Hong Kong Special Administrative Region and China. This will cause the simulation to run about eight to ten times before the entire cohort would be in the death state. Although such data could be used, a decrease in the cycle length would be a more descriptive choice.

In this simulation a cycle length of one year was chosen as in several similar studies [13], [139], [142], [143], [149], [152]. This will provide more data points from the simulation and will be able to generate a smoother survival curve. One year was also chosen above a five year period due to the effects of interventions. Pharmaceutical interventions are developed to have an impact within a short period of time, usually less than a year [58]. The annual risk adjustment for the interventions can be used in combination with the annual CHD risks in the simulation.

Each cycle of simulation results would represent one year of the individual's life. This will start at the *initial age* variable of the individual and continue until the simulation is complete. The initial age of the patient will influence the number of cycles performed throughout the simulation. A young initial age will require a large number of cycles to ensure that the entire cohort is absorbed in the death state.

A large number of cycles will ensure that the simulation continues until the end and does not stop while further cycles can be computed. If the number of cycles are insufficient to absorb the entire cohort, underestimations will be found [62], [143], [145]. The number of life years and costs will be inconclusive as the effects will be disregarded. The number of simulation cycles used can be concluded from the initial age, the cycle length and the life expectancy of the world population.

The lowest initial age that is viable to be simulated is 35 years. The risk of a person under the age of 35 experiencing a CHD event or dying of natural causes are below 0.08% [177]. This small risk will increase the number of cycles required without having a significant influence on

the final outcome. An individual at an age beneath 35 is regarded as healthy, unless exceptional conditions are observed [128], [178].

To make provision for a low initial age the number of cycles in the simulation will be 70. This is the same quantity of years as the world average life expectancy at birth. After a complete simulation of 70 cycles an individual of 35 will be at the age of 105 years. This is 48 years higher than the average life expectancy of a South African, and 21 years higher than China and Hong Kong SAR [181]. This will ensure that in all probability the entire cohort will be absorbed in the death state at the end of the simulation.

Approximately 12% of CHD events are fatal (*pDCHD*) within one year of the incident [13], [59], [179]. Mortality of CHD events has decreased during the past decade due to condition identification and medical treatment [176]. Interventions prescribed in this study do not change the risk of a fatal event. The interventions alter the risk of experiencing an event and therefore reduce the number of individuals dying from a CHD event.

The other probability that moves the cohort from any state to the death state is the *ndeath* variables. This represents deaths by causes unrelated to CHD events. The values obtained from the standard life tables are applied to the *healthy* state. In the *CHD* and *post-CHD* state these risks were doubled for the transition states. This increase is due to indirect damage caused by the CHD event experienced [132]. This means that the person in the *CHD* or *post-CHD* state will have twice the risk of an identical person in the *healthy* state.

As with the natural death risk of the individual, the probability of experiencing an additional CHD incident (*pACHD*) is also different from that of a healthy person (*pCHD*). This probability is adjusted as the risk of a CHD incident is different when an individual has already experienced one [13].

In this model further adjustments are made according to the individual risk of the person. The risk for a CHD event is multiplied by the personal relative risk (*PRR*) calculated from the biomarkers as in Equation 1.

$$PRR = RR_{i1} \times RR_{i2} \times \ldots \times RR_{in} \quad (1)$$

PRR - *Personal relative risk.*

RR_i - *Relative risk of the biomarkers identified*

This correlates the normal risk of the average healthy person to that of the individual. The risk of the each intervention alters the relative risk of the individual. The risk of dying from a CHD incident is however not changed when an additional event is experienced. This is due to the restrictions of Markov modelling [143].

Each cycle is independent of the previous cycles and previous cycles do not influence transition probabilities of a state. The probability of dying in the *CHD* state, will therefore remain constant even if previous events were experienced.

Another variable that remains specific to each state is the quality of life in the specific state. The quality of life in each state differs and is related to the conditions within the state. The quality in the *healthy* and *CHD* states are the highest and lowest respectively. The quality of life in the *post-CHD* state is higher than that of the *CHD* state. This is due to the intrusion a CHD event has on the everyday life of an individual. In the *CHD* state, the patient is required to go for regular check-ups and can sometimes be hospitalised for an extended period of time.

These quality adjustments are applied to the cohort within each state to obtain the quality adjusted life expectancy (QALE) of each cycle. The life expectancy (LE) of each cycle is the number in the cohort that remain outside of the death state at the end of the cycle. However, the quality of life of the living cohort needs to be adjusted to represent the different states in the model. The QALE of each cycle represents the number of the cohort outside of the death state that would have a perfect quality of life. Thus a 100% quality of life with no decreasing factors.

The same quality adjustments are applied to the life years (LY) of the cohort. The life expectancy of the cohort is discounted with the outcomes discount rate (*oDR*) to obtain the life years. A discount rate of 3% is used within this analysis [58], [120], [127], [132], [154]. Life years represent the outcome in terms of a net present value (NPV) [62]. The formula used for discounting the life expectancy is given by Equation 2.

$$LY = \frac{LE_t}{(1 + oDR)^t} \tag{2}$$

LY - *Life years at time zero.*

LE_t - *Life expectancy at time t.*

oDR - *Discount rate (%).*

t - *Time (years).*

The life expectancy at time t is discounted to give life years as the NPV. This discount is applied to every cycle to obtain the equivalent value of the life expectancy. QALE are discounted in the same manner as life expectancy. Quality adjusted life years (QALY), is the equivalent to a full life year at perfect living quality [62], [115], [143]. QALE are discounted to give the NPV of the life years, after it has been adjusted with the corresponding state quality. The QALY for the cohort will be used as one of the main outcomes for this study.

Movement from one state to another during a cycle, takes place through the transition states connected to it. The probability of an individual passing through a transition state is determined by the model variables and the probabilities assigned to a state. An *n x n* matrix is used to give all possible transitions and the respective probabilities. The transition matrix with the probabilities are shown in Table 6.

Table 6: Transition matrix for model states

Transition from	**To**				**Total**
	Healthy	**CHD**	***Post-CHD***	**Death**	
Healthy	1 -pCHD – nDeath	pCHD	0	nDeath	1
CHD	0	0	1 -pDCHD -nDeath	pDCHD +nDeath	1
Post-CHD	0	pACHD	1 -pACHD -nDeath	nDeath	1
Death	0	0	0	1	1

The transition matrix will be used to distribute the cohort throughout the model during each cycle as described in Chapter 2.3. The transition matrix is used to distribute the cohort between the model states, but does not quantify the distribution within each state. The distribution of the cohort is calculated using Equation 3 – 6 given in Table 7.

The distribution equations are derived from the transition matrix. It uses the previous distribution to calculate the new one, based on the transitions made. Continuous distribution gives a profile of each state and can be used to establish a survival curve for the cohort. The curve show the distribution of the states at a certain time. From the survival curve several other deductions can be made. One such deduction is the main state in which an individual would be most likely to spend a year of the simulation.

Table 7: Cohort distribution equations

Model state	Distribution equation	
Healthy	$Healthy_t = Healthy_{t-1} \times \left(1 - \left(pCHD \times (1 - effect)\right) - nDeath\right)$	(3)
CHD	$CHD_t = Healthy_{t-1} \times pCHD \times \left(1 - effect_p\right) + PostCHD_{t-1} \times pACHD \times (1 - effect)$	(4)
Post-CHD	$PostCHD_t = PostCHD_{t-1} \times \left(1 - nDeathp - \left(pACHD * (1 - effect_s)\right)\right) + CHD_{t-1} \times (1 - pDCHD - nDeathp)$	(5)
Death	$Death_t = Death_{t-1} + Healthy_{t-1} \times nDeath + CHD_{t-1} \times (pDCHD + nDeathp) + PostCHD_{t-1} \times nDeathp$	(6)

Healthy, denotes the number of the cohort in the healthy state at time t; $Healthy_{t-1}$, at time t-1; CHD_t, cohort in CHD state at time t; CHD_{t-1}, at time t-1; *Post-CHD*$_t$, cohort in *post-CHD* state at time t; $PostCHD_{t-1}$, at time t-1; *Death*, cohort in death state at time t; $Death_{t-1}$, at time t-1; *effect* the effectiveness of an intervention for primary prevention; $effect_s$ the effectiveness of an intervention for secondary prevention; *pCHD*, probability of a CHD incident; *pACHD*, probability of an additional CHD incident; *pDCHD*, probability of death from a CHD incident; *nDeath*, natural death probability; *nDeathp*, natural death probability after a CHD incident.

This provides information that can be compared to other similar situations with comparison between the status quo and the interventions. This information can also be used to indicate how fast or slowly any intervention would impact the survivability of an individual. A slow working highly effective intervention can be compared to a rapid intervention with a lower effectiveness. The information from the status quo distribution will be the baseline to which the interventions will be compared.

The results from the base case cohort simulations will be compared to Monte Carlo simulations for a large population. During the Monte Carlo simulations the values of the variable will be changed and stochastically chosen. For the status quo Monte Carlo simulations, some of the variables will be randomised while others remain constant throughout the entire series. A list of the randomised variables are given in Table 8.

The *size*, *cycle length* and *oDR* parameters are not randomised from the initial values. Changing these parameters changes the design of the model and would give results that are incomparable to the results of the cohort simulation. The personalised relative risk (*PRR*) and *age* are parameters related to the specific individual who is simulated. Varying these parameters changes the individual and not the model parameters.

Table 8: Monte Carlo simulation parameters for the status quo simulations

Variable	Low value Lower limit of the 95% confidence interval	High value Upper limit of the 95% confidence interval	Estimated standard error	Distribution	Alpha Alpha parameter for distribution determined by methods of moments	Beta Beta parameter for distribution determined by method of moments	Ref.
qHealthy	0.94	0.97	0.166	Beta	46.439	0.024	[132], [138]
qCHD	0.75	0.88	0.033	Beta	115.580	28.895	[13], [124], [125], [132], [138]
qPCHD	0.8	0.91	0.028	Beta	136.776	24.137	[13], [132]
pCHD	0.09	0.11	0.005	Beta	345.631	3110.682	[13]–[15], [59], [178]
pDCHD	0.10041	0.12272	0.006	Beta	341.240	2717.564	[13], [59], [176], [179]
pACHD	0.02594	0.03171	0.001	Beta	372.525	12548.910	[13], [152], [153], [176], [180]

Keeping the individual constant is important since the purpose of this study is to provide individual specific results. During the Monte Carlo simulations, the purpose is to simulate the same individual in a number of different living conditions. These living conditions are generated by the model parameters being varied. Variations in the individual's parameters will therefore simulate several different individuals in a number of living conditions. Comparing these results would yield inconclusive results on a personalised level.

Monte Carlo simulations will be repeated 10 000 times. This value was chosen to generate a sample population the same size as the cohort. The Monte Carlo population will each be run through the cohort system. Only the final results from the cohort simulation will be recorded. These results include the QALY of the simulated cohort. After recording the results, a new set of parameters will be generated and simulated as a cohort. This will be done until 10 000 scenarios are generated.

Randomised parameters will be generated with constraints as in Table 8 from a defined distribution. The initial values are the values obtained from literature and given in Table 5. Low and high values are the lower and upper limit values of the 95% confidence interval respectively. The high and low values were used to estimate the standard error (est. se.) of the range by using Equation 7 [143].

$$est.se. = \frac{high - low}{2 \times 1.96} \tag{7}$$

$est.\ se.$ - *Estimated standard error.*

$high$ - *Upper limit of 95% confidence interval.*

low - *Lower limit of 95% confidence interval.*

Statistical functions in Microsoft Excel™ are used to generate a stochastic value for each parameter. The mean value, estimated standard error and distribution parameters are inserted into the functions to obtain a random value. Excel's gamma and beta distribution inverse functions (GAMMA.INV and BETA.INV) are used to sample values from the distribution. Parameters for the beta and gamma distribution are calculated with Equations 8 – 11.

Beta distribution

$$\alpha = \mu \left(\frac{\mu(1-\mu)}{\sigma^2} - 1 \right) \tag{8}$$

$$\beta = (1-\mu) \left(\frac{\mu}{\sigma^2}(1-\mu) - 1 \right) \tag{9}$$

Gamma distribution

$$\alpha = \frac{\mu^2}{\sigma^2} \tag{10}$$

$$\beta = \frac{\sigma^2}{\mu^2} \tag{11}$$

α - *Alpha parameter of the distribution.*

β - *Beta parameter of the distribution.*

μ - *Mean/Initial value of the distribution.*

σ - *Standard error of the distribution.*

Values of utilities and transition probabilities are constrained within the interval 0 and 1. These parameters were assigned beta distributions, due to the flexibility of the distribution. The relative risk of the individual is greater than 0 and not constrained by an upper limit [13], [29], [61], [132], [142]. All relative risks and cost values follow a gamma distribution in the study. Costs and relative risks are commonly skewed to the right and therefore they are assigned to the aforementioned distribution [29], [61], [132], [138], [142]. All the parameters are varied simultaneously to generate results for the simulation.

Results from the Monte Carlo population are analysed to make the results comparative to that of the cohort simulation. The following statistical indicators will be calculated: mean, median, minimum, maximum, standard deviation, the 2.5% percentile and the 97.5% percentile. These will be used to give an indication of the population distribution. The statistical results will be compared to the single cohort simulation. It is expected that the cohort result would differ from the Monte Carlo simulation, but by a relative small margin.

The status quo of the study will consist of results from the cohort and Monte Carlo simulations. Both the above mentioned simulations will generate QALY results without interventions influencing the outcome. This will be used to compare results from similar simulations when interventions are added to the model.

2.5 Intervention simulation and assumptions

CHD interventions all have the common purpose of lowering the risk of experiencing a CHD event. Each intervention influences a certain aspect of an individual's body and induces some form of change. The most common influences are shown in the overall CHD system as described in section 1.2. These interventions will be simulated through a similar process as the status quo.

The same model that was used to simulate the status quo cohort will be used to simulate each intervention. Additional parameters, relevant to the intervention, are added to the model during the simulation. The main additional parameters include the relative risk of the intervention, intervention adherence, effectiveness and the quality of life changes when an intervention is applied. These parameters will be added to the simulation model for primary and secondary prevention, while the parameters of the status quo remain unchanged.

Each intervention will be simulated individually and not as a combination of interventions. This method was chosen as the individual influence of each intervention is desired in the study. It is expected that certain combinations of interventions will have a more positive effect than only

a single intervention [58], [111]. Combinations will not be analysed as it is outside the scope of this study. Possible combinations could, in some cases, be recommended from the results.

The effectiveness of each intervention is determined by the relative risk for CHD (*RR*) and the intervention adherence. Each intervention's relative risk is given in Table 2 of section 1.2. These values are combined with the intervention's adherence to calculate an effectiveness for the intervention. This effectiveness is applied in the distribution equations 3 - 5, as the *effect* variable. This changes the risk of the individual experiencing a CHD incident. Intervention effectiveness is calculated using equation 12 below [29].

$$effect = RR_i \times IAdh \tag{12}$$

$effect$ - *Intervention effectiveness.*
RR_i - *Relative risk for CHD of intervention* i.
$IAdh$ - *Intervention adherence.*

The effectiveness of an intervention is strongly related to the adherence thereto. Relative risk alterations will not be as influential as possible if the intervention is not adhered to. Intervention adherence is generalised for this study based on the type of the interventions. All interventions are pharmaceutical therapies or drugs, and are therefore treated as the same type.

The adherence value for all the drugs is kept the same. Adherence of 50% (CI, 45-56) and 66% (CI, 56-75) were found for primary and secondary prevention respectively. This adherence includes neglecting to comply with the intervention prescription. According to Naderi *et al.*, adherence decreases by 0.15% points per month of follow up [182]. However, this is not added to the simulation model, due to the 'Markovian assumption' [143], stating that the current cycle is independent of previous cycles.

Adherence is not dependent on drug classes, age, gender or the payment method [182]. However, each intervention would change the normal quality of living to some extent. Quality of life adjustments are added for each intervention in the model states. These adjustments are applied due to the changes that an individual would experience when following an intervention. This also accounts for the inconveniences of following an intervention as prescribed.

Adjustments to the quality of life reflect in the number of QALY in the results. QALY for each intervention will be compared to the results from the status quo. This comparison will quantify the intervention's effect and reflect on its effectiveness. Interventions will show a positive effectiveness if the QALY after the simulation is higher than that of the status quo. Results for the interventions will be generated by using both simulation types, as in the status quo.

Cohort and Monte Carlo simulations will be performed on each intervention in order to compare results with the baseline values. The Monte Carlo simulations follow the same procedure as the status quo. Intervention parameters are kept the same for the Monte Carlo simulation, but certain values are randomised for each simulation. Randomised variables are generated from a given range during each simulation.

Table 9: Pharmaceutical intervention parameters for Monte Carlo simulation

Drug class	**Low RR value** Lower limit of the 95% confidence interval	**High RR value** Upper limit of the 95% confidence interval	**Estimated standard error**	Distribution	**Alpha** Alpha parameter for distribution determined by methods of moments	**Beta** Beta parameter for distribution determined by method of moments	Ref.
Statins:	0.76	0.8	0.010	Gamma	5842.859	0.00013	[6], [74]–[84]
Salicylates:	0.75	0.9	0.038	Gamma	459.199	0.0018	[74], [75], [84], [85]
Indirect thrombin inhibitors:	0.84	0.98	0.036	Gamma	649.207	0.0014	[75], [84]
Direct thrombin inhibitors:	0.59	0.98	0.099	Gamma	58.352	0.0130	[74], [84]
ACE inhibitors:	0.71	0.88	0.043	Gamma	331.828	0.0024	[84], [86], [87]
Angiotensin-renin inhibitors:	0.87	0.97	0.026	Gamma	1300.564	0.0007	[88]
β-blockers:	0.59	0.82	0.059	Gamma	138.292	0.0049	[75], [84], [87], [89]
Calcium channel blockers:	0.67	1.03	0.092	Gamma	81.678	0.0102	[75], [84], [87], [89]
Diuretics:	0.69	0.92	0.058	Gamma	181.282	0.0044	[84], [90], [91]
Antidepressants:	0.44	0.52	0.020	Gamma	553.170	0.0009	[51], [52], [92]–[99]
Biguanides:	0.62	0.89	0.069	Gamma	115.423	0.0064	[75], [100]–[103]
α-glucosidase inhibitors:	0.16	0.8	0.163	Gamma	5.135	0.0720	[104]
Ethanol:	0.66	0.77	0.028	Gamma	640.158	0.0011	[86], [105]–[108]

Table 9 gives the relative risk parameters of each intervention for the Monte Carlo simulations. The low and high RR values were obtained from the confidence interval as in Table 2. The same randomisation process is used to generate values as during the status quo simulations. The parameters of the status quo are kept the same until all the simulation cycles have been

completed before a new set of randomised variables are generated. This ensures that all interventions and the status quo are simulated with the same base variables.

Statistical analysis of the simulation results is performed in order to make comparisons between the results. Results from the Monte Carlo simulations are compared to the cohort results to verify that it does not differ significantly. Comparison between the Monte Carlo simulations of the status quo and interventions, is outside of the scope of this study as it represents a population and not an individual. Monte Carlo simulations are therefore done to ensure that the cohort results would in all probability represent a true reflection of results.

Results from the status quo and the intervention simulations gives a quantification on the effectiveness of preventing CHD incidents. This can be used as a basic indication of what intervention would be most beneficial for the individual. The effectiveness needs to be combined with the costs and economic impact of such an intervention. Such combination will provides an optimised prescription for the individual.

2.6 Cost-effectiveness analysis

Cost effectiveness of any intervention and lifestyle, plays a role in the prescription choices that are made. For this reason the cost-effectiveness analysis is a fundamental part of prescribing interventions to an individual. In this section the process of completing a cost-effectiveness analysis for the simulations is described. The cost-effectiveness analysis is performed on both the status quo and the intervention simulations.

Each state in the model has a cost related to CHD incidents that needs to be paid by an individual. Several factors influence this and need to be specified in order to calculate the costs. In the simulation the main factors for this study are contained within the different states. Costs within the model are limited to costs related to CHD incidents. A base cost is assigned to each state from literature, representing the cost of staying in that state for one simulation cycle. The cost differs based on the health conditions and medical activity of the state.

Costs in the *healthy* state are the lowest as the individual remains healthy and medical attention is done routinely. In the *CHD* state the cost is higher due to factors related to the CHD incident. The individual receives immediate medical attention after the incident and routine follow-ups raise the medical costs. In the *post-CHD* state, the cost is lower than that of the *CHD* state, but higher than in the *healthy* state. Routine check-ups and assessment tests are performed more frequently and therefore increases the cost.

There is no cost applied to the *death* state, unlike the other states. However there is a cost associated with the process of dying. During each cycle, a cost is added for each individual that passes through any transition pathway to the death state. These are costs related to post-mortems, funerals and other death related processes. This cost is only applied once for each individual within the cohort, but during different cycles.

All costs are calculated at the end of each simulation cycle. Costs are applied to the cohort distribution within the respective states. The states' costs are added to calculate a total for each cycle and accumulated until the end of the simulation. A cost per individual is calculated and used to compare the different simulations with one another. Costs for each of the modelling states are given in Table 10.

Table 10: Base costs for health states

Variable	Value (Int$)	Description	References
cHealthy	79	Cost for staying one cycle in the healthy state.	[132]
cCHD	27 921	Cost for one cycle in the CHD state.	[13], [29], [124], [125], [132], [154]
cPCHD	3 647	Cost of one cycle in the *post-CHD* state.	[13], [29], [113], [124], [125], [132]
cDeath	4 227	Cost of moving to the death state by any transitional pathway.	[29], [124], [125]

Costs for the base case are only dependent on the base cost of each state and not influenced by the costs of interventions. This indicates the cost while using no interventions to alter the risk of a CHD incident. Costs related to interventions are added additionally during the simulation. The difference between the costs gives an indication of what costs the intervention would add for an individual. For each intervention an annual base cost value is applied within the simulation. These costs are indicated in Table 11.

South African wholesale drug prices (Table 11) are used to calculate the cost value for each intervention. Daily dosages are multiplied by the number of days (365 days) to determine the annual requirements for each drug. Available package sizes and respective prices are used to estimate the annual cost for the intervention.

Table 11: Base costs for interventions

Drug Class (Example)	Cost value p.a. (Int$)	Daily dosage	Unit Quantity	Unit price	Ref.
Statins (Lipitor)	727	40 mg	30 x 80 mg	R 304.61	[183]
Salicylates (Dispirin)	44	300 mg	96 x 300 mg	R 59.99	[184]
Indirect thrombin inhibitors (Cipla-Warfarin)	85	5 mg	100 x 5 mg	R 118.82	[185]
Direct thrombin inhibitors (Pradaxa)	1 869	300 mg	60 x 150 mg	R 782.76	[186]
ACE inhibitors (Lizro)	160	20 mg	30 x 20 mg	R 67.37	[187]
Angiotensin-renin inhibitors (Diovan)	326	160 mg	28 x 320 mg	R 255.35	[188]
β-blockers (PurBloka)	102	320 mg	1000 x 40 mg	R 188.92	[189]
Calcium channel blockers (Adalat)	1 220	40 mg	60 x 20 mg	R 510.71	[190]
Diuretics (Hexazide)	27	25 mg	100 x 25 mg	R 38.59	[191]
Antidepressants (Zoloft)	714	50 mg	30 x 50 mg	R 299.13	[192]
Biguanides (Glucophage)	110	1500 mg	300 x 1000 mg	R 307.24	[193]
α-glucosidase inhibitors (Glucobay)	792	300 mg	90 x 100 mg	R 331.56	[194]
Ethanol (Red wine)	1 270	190 ml	750 ml	R 70.00	Assumption

The estimated costs are converted to international dollars with the purchasing power parities (PPP) conversion factor for the published year and country. All costs are adjusted to the end of 2014 by using the annual CPI inflation of South Africa [195]. This will adjust all costs to international dollars at the end of 2014. These adjusted values are added to the simulation and will determine the intervention specific cost at the end of the simulation.

As with the benefits, the costs are discounted at the end of each simulation cycle. The costs are discounted at the same rate of 3% as in the current guidelines for cost-effectiveness analysis [58], [120], [127], [132], [154]. Costs are discounted to give the net present value (NPV) of the intervention after a simulation cycle. The NPV of each intervention is compared to the NPV of the status quo. A NPV higher than the status quo will indicate higher costs and should be kept to a minimum.

By using the NPV of each simulation the cost-utility analysis is done. The Int$/QALY is determined for each simulation to quantify the cost effectiveness. This indicates the cost of

adding a perfect life year by following the simulated situation. According to similar studies and current guidelines, an incremental cost effectiveness ratio (ICER) of less than the GDP per capita is, “highly cost effective”. An ICER between one and three per-capita GDP is considered to be “cost effective” while anything above this is deemed “not cost-effective” [8], [58], [118], [196].

ICER is the difference in the intervention cost per QALY compared to that of the status quo [8], [62], [115], [118], [126], [136], [137], [139], [143]. Equation 13 is used to calculate the ICER for each intervention that is simulated. Interventions with a lower cost and better effectiveness are said to dominate and would be the preferred treatment. Inferior interventions have a higher cost as well as a lower effectiveness compared to the baseline. Interventions are commonly more expensive and more effective or vice versa, relative to the base case. Final judgment should be made on whether the cost or the effectiveness carries the most weight for the individual.

$$ICER = \frac{Cost_i - Cost_s}{QALY_i - QALY_s} \tag{13}$$

$Cost_i$ - Cost of intervention *i* (Int$)

$Cost_s$ - Cost of status quo (Int$).

$QALY_i$ - Quality adjusted life years of intervention *i* (years).

$QALY_s$ - Quality adjusted life years of status quo (years).

Judgement on what intervention yields the best solution can additionally be based on results from the Monte Carlo simulations. Cost parameters are added to the Monte Carlo simulations, generating data on the cost for the simulated population. This data, in a similar manner to the QALY results, are only compared to the results of the respective intervention and not analysed with the status quo.

Costs variables are randomly generated from a possible range of values (Table 12). These values are obtained by increasing and decreasing the costs by 30%. These are run through the simulation and the costs for each simulation are calculated. Results from the statistical analysis on the data, are compared to the results from the cohort simulation. This comparison indicates if the cohort simulation for an individual would be related to the results from a random population.

Table 12: Cost variables for the Monte Carlo simulations

Cost variable	**Low value (Int$)** 30% decrease of initial value	**High value (Int$)** 30% increase of initial value	**Estimated standard error**	**Distribution**	**Alpha** Alpha parameter for distribution determined by methods of moments	**Beta** Beta parameter for distribution determined by method of moments
cHealthy	55	102	12.09	Gamma	42.68	1.85
cCHD	19 544	36 297	4 273.70	Gamma	42.68	654.15
cPCHD	2 553	4 741	558	Gamma	42.68	85.45
cDeath	2 959	5 495	647.07	Gamma	42.68	99.04
Statins:	509	945	111.37	Gamma	42.68	17.05
Salicylates:	31.35	58	6.85	Gamma	42.68	1.05
Indirect thrombin inhibitors:	59	110	13.03	Gamma	42.68	1.99
Direct thrombin inhibitors:	1 308	2 430	286.21	Gamma	42.68	43.81
ACE inhibitors:	112	209	24.63	Gamma	42.68	3.77
Angiotensin-renin inhibitors:	228	424	50.02	Gamma	42.68	7.66
β-blockers:	75	140	16.58	Gamma	42.68	2.54
Calcium channel blockers:	854	1 586	186.74	Gamma	42.68	28.58
Diuretics:	19	35	4.23	Gamma	42.68	0.65
Antidepressants:	500	928	109.38	Gamma	42.68	16.74
Biguanides:	77	143	16.85	Gamma	42.68	2.58
α-glucosidase inhibitors:	554	1 029	121.23	Gamma	42.68	18.56
Ethanol:	889	1 652	194.52	Gamma	42.68	29.77

Costs for the states are randomised within the gamma distribution and kept the same for all the interventions for one complete simulation. Thereafter a new set of values are generated and simulated. Costs from the status quo and interventions are statistically analysed to understand the data and make comparisons. This analysis and simulations do not give the effect of a single parameter on the simulation. The effect that each distinct variable has on the total simulation, is determined by performing a sensitivity analysis.

2.7 Sensitivity analysis

Variables can constantly change and would therefore impact the result of the study. The results of the model are subject to the randomness and uncertainty of the variables. The magnitude to which a specific variable would influence the results is expressed through a sensitivity analysis. Understanding the impact of each variable will ease the process of decision making, as assumptions can be compared to each other.

One-way and probabilistic sensitivity analyses are performed in this study. One-way sensitivity analysis varies each parameter separately and independently from the others. This indicates how the parameter will influence the model results if all other variables remained the same. With a probabilistic sensitivity analysis all parameters are varied simultaneously using probability distributions. This generates a sample distribution and is used to estimate confidence intervals for the model. [143]

A generic intervention based on average values was created for the sensitivity analysis. This represents a summary of the interventions and the base case combined into a singular case. Base modelling parameters are kept the same as in all the simulations. Only intervention specific variables were changed and not related to a single intervention. The generic intervention is not a specific combination of variables, nor is it a proposed intervention.

The variables that are changed for the generic intervention are; intervention costs, intervention relative risk, and the quality adjustment for discomfort due to the intervention. The variables are determined by using all the interventions' values for the respective variable. The lowest and highest value were taken from the list of interventions for each variable, and used as the upper and lower limit of the variable respectively. The average between the two limits is used as the initial value during simulations.

Initial values for the other parameters are the same as is used for the base case and intervention simulations. The generic intervention provides a reference point for all the variables that would influence the model. The generic intervention is compared to the status quo to obtain an ICER that is used to analyse the variables. This is done for both the one-way and the probabilistic analyses.

In a one-way sensitivity analysis, one parameter is varied separately and independently from the others. The value is firstly changed to the lower limit of the confidence range. The model is simulated with the applied value and a result is calculated. After the simulation has been completed, the variable is changed to the upper limit of the confidence range and simulated

again. The variable is restored to its initial value and after which the process is repeated for the following variables [154].

This analysis gives a distribution of the results that can be obtained with the minimum and maximum values of a variable. The spread of the results indicate the magnitude of impact the variable has on the model. From this it could also be concluded which variables are more influential factors in deciding which intervention is best for an individual.

The probabilistic sensitivity analysis is similar to the Monte Carlo simulations that are done throughout the study. All variables are simultaneously varied within a given distribution, simulated, and repeated several times. To do a probabilistic sensitivity analysis on all the interventions, is the generic intervention scenario used as reference. The generic intervention and other parameters are run through a complete Monte Carlo simulation. Parameter uncertainty and the correlation between the parameters can be evaluated.

Results from the simulation provide an indication of the probability that an intervention would be cost-effective or not. Cost-effectiveness acceptability curves compared with the willingness to pay are generated from the results. This shows how likely it is that the payers would pay for an intervention. Confidence intervals are furthermore determined from the results and give an indication of the data distribution.

For the sensitivity analyses all the main parameters are varied and evaluated. Transition probabilities related to the disease and mortality are evaluated, but those for the death by other causes are kept constant throughout. Death by other causes influences the results but is not related to CHD and therefore outside the scope of the study. The patient's relative risk, CHD risk, additional CHD risk, as well as death by CHD events forms part of the analyses.

Parameters associated with the model states influence the outcomes based on two main parameters. Quality adjustments and costs for staying in a state directly influences the outcome of the study and results. The analysis of these gives an indication on how the model states influence the outcome of the simulation. By knowing the influences of these variables, it is possible to assess how robust the model structure is.

Interventions do not cause a change in model structure, but influence some of the health states. The relative risk, adherence rate, intervention costs and quality adjustments, influences the cohort distribution. This is especially applicable in the *healthy* and *post-CHD* states, in which the interventions are followed. Each intervention will impact the study differently based on the values of the respective parameters. A sensitivity analysis is not performed on each individual intervention, but rather on the intervention parameters.

Intervention variables are captured in the generic intervention and given in Table 13. This allows the evaluation of the parameter and not the intervention itself. Transition probabilities and utilities are drawn from the beta distribution, while the gamma distribution is used for costs and relative risks. The model parameters for the sensitivity analyses are varied between the respective ranges as given in Table 8, Table 9 and Table 12.

Table 13: Generic intervention parameters for sensitivity analysis

Drug class	**Initial value**	**Low value** Lower limit of the 95% confidence interval	**High value** Upper limit of the 95% confidence interval	**Estimated standard error**	**Distribution**	**Alpha** Alpha parameter for distribution determined by methods of moments	**Beta** Beta parameter for distribution determined by method of moments
Cost:	Int$ 573	Int$ 401	Int$ 744	87.71	Gamma	42.68	13.42
Relative risk:	1.14	1.00	1.29	0.07	Gamma	237.45	0.005
Quality adjustment:	0.001	0.000	0.002	0.0005	Beta	3.83	3 832.78
Primary adherence	0.5	0.45	0.56	0.028	Beta	158.24	158.24
Secondary adherence	0.66	0.56	0.75	0.048	Beta	62.38	32.14

2.8 Summary

Optimising interventions for coronary heart disease is a process which focusses on the individual. Biomarkers are measured and evaluated to identify the risk indicators for CHD. Interventions affect each biomarker in a different way and allows for a personalised prescription. Interventions influencing the identified biomarkers are listed, reducing the available spectrum to a defined few.

Interventions are simulated with a Markov model [145] to establish their respective influences. Cohort and Monte Carlo simulations are performed to compile a status quo for comparison between the interventions. The effectiveness of the interventions are expressed as the QALY that were added to the baseline simulation and prolonging the life of the individual. The effectiveness provides an idea as to what intervention should be followed.

Minimising the costs of the intervention will be beneficial for the individual and should therefore be determined. Costs are calculated for the simulation and evaluated with the effectiveness to yield the cost-effectiveness of each intervention. Uncertainty arising from the results are quantified with a one-way and probabilistic sensitivity analysis. Personalised cost-effective interventions for the individual are identified with a reasonable probability of decreasing their CHD risk.

CHAPTER 3 – RESULTS AND DISCUSSION

3 Results and discussion

3.1 Biomarker analysis

Every individual is different and is defined by unique biological characteristics. These biological characteristics can be quantified and expressed by measuring a patients biomarkers. Biomarkers represent the individual's health condition and can be used to represent the patient's relative risk of experiencing a CHD event.

Blood tests of two individuals were analysed as case studies for the cost-effectiveness study of CHD interventions. Blood test results quantify the biomarkers and these results are shown in Table 14. Dissimilar blood tests were performed on the two patients, due to different testing objectives. Risk identification for CHD events was included in these objectives, but was not necessarily the main focus point.

The main difference between the two case studies is the biomarkers that were analysed. In both case studies six biomarkers analysed were compared. Biomarkers were tested as part of a routine health visit to a general practitioner. This represented each patient's generalised risk for CHD as well as other medical diseases. However, in case study 2 biomarkers for inflammation and renal functions were analysed instead of those for vascular functions.

Test results were analysed and indications were given regarding which biomarkers should be focussed on. Biomarkers with a tick mark (✓) were found to be within the healthy range of values. Such biomarkers indicated no distinct CHD risk to the patient. Biomarkers outside of the healthy range were identified by a cross (X) and were used to continue the study. Biomarkers with a relative risk smaller than one, such as HDL and IGF-1, were treated as exceptions to this rule. These were added to the identified biomarkers if the results were within the healthy range, since they decrease the risk for CHD significantly.

Results for case study 1 were obtained from blood tests of a 53 year old female. The patient had elevated triglyceride and insulin resistance values. Interpretation of the results reported by the laboratory as well as the prognosis arrived at by the simulation indicated that these values were outside of the healthy range. This is associated with an increased risk for CHD and was identified as requiring treatment. HDL was above the minimum value and therefore was added to the biomarkers influencing the patient's risk.

Table 14: Serum blood test results of patients

	Case Study 1			Case study 2		
Patient Details	**Test results**	**Laboratory prognosis**	**Simulation prognosis**	**Test results**	**Laboratory prognosis**	**Simulation prognosis**
Gender:	Female			Male		
Age:	53			58		
Height (cm):	170			180		
Weight (kg):	110			75		
Lipid-related markers:						
Triglycerides	2.25 mmol/l	X	X			
LDL	3.07 mmol/l	✓	✓	5.1 mmol/l	X	X
HDL	1.01 mmol/l	✓	✓	1.7 mmol/l	✓	✓
ApoB	-					
Leptin	-					
Inflammation markers:						
hsCRP	-			3.1 mg/l	X	✓
IL-6	-					
TNF-α	-					
GDF-15	-					
OPG	-					
Marker of oxidative stress:						
MPO	-					
Marker of vascular function and neurohormonal activity:						
BNP	-					
Homocysteine	8.5 µmol/l	✓	✓			
Coagulation marker:						
Fibrinogen	-					
Necrosis marker:						
Troponins	-					
Renal function marker:						
Urinary ACR	-			4.0 mg/g	✓	✓
Metabolic markers:						
HbA1c	5.4 %	✓	✓	5.5 %	✓	✓
IGF-1	-					
Adiponectin	-					
Cortisol	-					
BDNF	-					
Insulin resistance (HOMA)	4.11 units	X	X	0.35 units	✓	✓

HDL denotes high-density lipoprotein; BNP, B-type natriuretic peptide; ACR, albumin–to-creatinine ratio; GDF-15, growth-differentiation factor-15; LDL, low-density lipoprotein; HbA1c, glycosylated haemoglobin A1c; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor-α; ApoB, apolipoprotein-B; IGF-1, insulin-like growth factor-1; MPO, myeloperoxidase; OPG, osteoprotegerin; BDNF, brain-derived neurotrophic factor; HOMA, homeostasis model assessment.

Case study 2 provided detailed results of a 58 year old male. Six biomarkers were analysed, of which three were added to the list for observation. Similarly, as with case study 1, HDL was also added, due to the beneficial influence it has. The other biomarkers identified for case study 2 were LDL, CRP and HDL.

Biomarker prognosis for the lists in both cases were similar for the laboratory and simulation analysis. The single exception was found with CRP being relatively close to the limits in case study 2. This indicates that both could have been used to compile the lists without the other one. A validation check for the lists are therefore done to ensure that they are a representation of the patient. These lists are given in the first column of Figure 14 and Figure 15 and arranged according to biomarker's relative risk. Interventions suitable for each biomarker were added to the list in the following section before the survival simulation was performed.

3.2 Identified interventions

Preventative interventions are prescribed based on indications or conditions related to the risk of CHD. Preventative strategies are identified by establishing the influence of interventions on a specific biomarker. Biomarkers are filtered based on their values and listed to ensure only those with a significant influence are treated. Interventions for each listed biomarker are identified in this section.

Biomarkers identified in each case study are detailed in the first column of Figure 14 and Figure 15. Each biomarker was analysed using Table 4 based on the interconnected influences of interventions. Results from the analysis were combined with the biomarker list to indicate the appropriate interventions (Figure 14 and Figure 15) for the case studies.

These lists indicated which intervention would have had the largest impact on the relative risk for CHD. Interventions that would influence the respective biomarker were listed according to the CHD relative risk modification. The interventions were listed according to their effect on CHD risk and not on the biomarker values. The drugs with the lowest relative risk were listed first and the remaining classes were listed in an ascending order. This indicated to the patient or medical professional what intervention would have had the best influence on CHD by affecting a biomarker in question.

In both lists one or more prominent biomarkers could be identified. These biomarkers were affected by a large number of interventions, while being high up on the list thereby indicating where the focus should have been when deciding which biomarkers would receive the most attention.

Insulin was listed first in case study 1 and was the biomarker with the highest number of possible interventions. In case study 2, LDL was similarly listed with influences from several interventions. These indicators were used to identify the interventions to be used in the modelling phase of this study.

For case study 1, thirteen interventions influencing insulin were identified based on the list (Figure 14). These interventions were verified visually with Figure 16 and found to be the same. Figure 16 showed that insulin was connected to all the interventions and health factors of the model. This large number of interventions indicated that insulin is required in several functions throughout the human body. Interventions affecting insulin would thus change the risk of CHD based on its overall impact and not on the direct change to insulin.

LDL was identified as the most prominent biomarker in case study 2. This was associated with four interventions. Figure 17 shows that LDL was influenced by antidepressants, alcohol consumption, biguanides, and statins. This indicated that it would be possible to limit the interventions to only a few, in contrast case study 1. A biomarker specific approach was followed for simulating case study 2, due to the limited treatment possibilities. Influences were more specific and directed towards the biomarker. Interventions would thus change the biomarker swiftly and consequently the risk for CHD.

Both lists and visualisations showed that identifying interventions were necessary before simulations were conducted. They showed that the number of interventions were different for the prominent biomarkers. Such differences indicated that the change in CHD risk was due to either biomarker specific influences or general systematic changes. Interventions associated with the prominent biomarkers were henceforth used in the survival and cost simulations.

Biomarker	Pharmaceuticals
Insulin	α-glucosidase inhibitors
	Antidepressants
	β-blockers
	Alcohol consumption
	Biguanides
	Direct thrombin inhibitors
	Statins
	ACE inhibitors
	Diuretics
	Salicylates
	Calcium channel blockers
	Indirect thrombin inhibitors
	Renin inhibitors
Triglycerides	Antidepressants
	Biguanides
	Statins
HDL	Antidepressants
	Alcohol consumption
	Biguanides
	Statins

Figure 14: Generated biomarker and intervention prognosis - case study 1

Biomarker	Pharmaceuticals
LDL	Antidepressants
	Alcohol consumption
	Biguanides
	Statins
CRP	Biguanides
	Statins
HDL	Antidepressants
	Alcohol consumption
	Biguanides
	Statins

Figure 15: Generated biomarker and intervention prognosis – case study 2

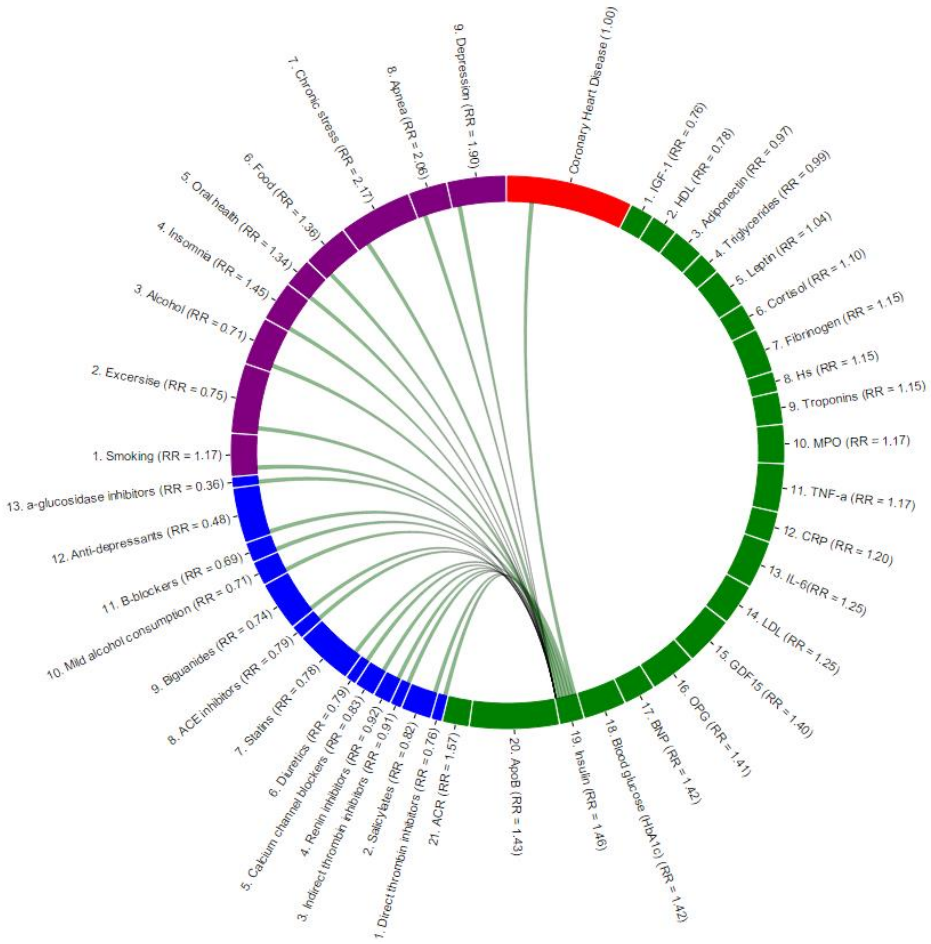


Figure 16: Visualisation of interventions associated with insulin

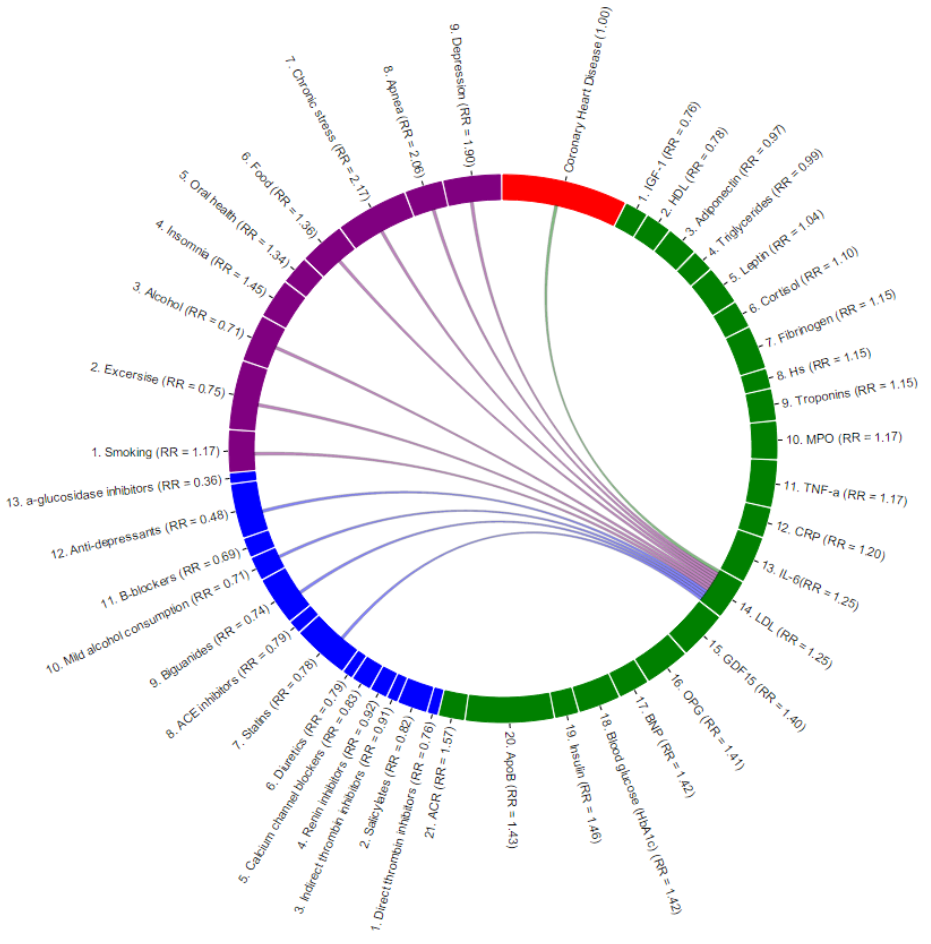


Figure 17: Visualisation of interventions associated with LDL

3.3 Simulation model evaluation

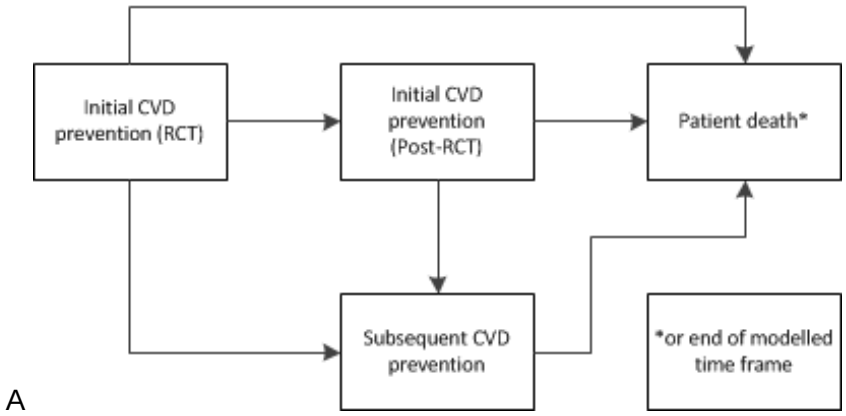
A relevant model forms the foundation of the study and provides accurate results to base conclusions on. Such a model was developed in Chapter 2.3 and given in Figure 9. Comparison with other models used for similar studies highlights the main, as well as additional, components. In this section, two models are used to validate the design of Figure 9 and to establish the differences between these models.

Figure 18 shows the Markov models used in two cost-effectiveness studies done on CHD and pharmaceutical interventions. Both studies focussed on the cost-effectiveness of statins as an intervention for prevention of CHD. Figure 18A compares the cost-effectiveness of a single drug to two generic drugs in a population at high risk of CVD events [124]. Figure 18B studied a population of patients diagnosed with type 2 diabetes and the cost-effectiveness of statins when used for primary CHD prevention [29]. The basis for both the models remains the same and illustrates how Markov models are used for CHD simulations.

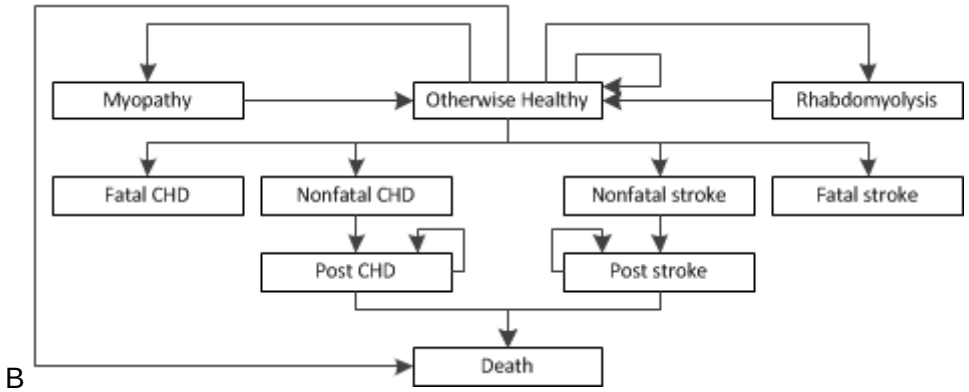
Figure 9 consists of four main model states, *healthy*, *CHD*, *post-CHD* and *death*. These states are found in either one or both of the models. Initial analysis indicates that this study's model is a combination of those similar to it. It is important to understand the difference between the models before a judgement can be made.

Figure 18A consists of four main states in the model, with three of them similar to those in Figure 9. Both of the *initial CVD prevention* states are similar to the first state (*healthy*), but the intervention is applied differently by Gandhi *et al.* [124]. Patients were part of a randomised control trial (RCT) for primary prevention during the phase in which they would be deemed healthy. Some patients ended their participation in the RCT at a certain point during the study, moving the patients to the second group. In this group they remained healthy, but the intervention was no longer prescribed for preventative measures.

Interventions are prescribed throughout the *healthy* state in this study and not limited to a RCT. The same approach is used by De Vries *et al.* [29] in the *otherwise healthy* state. Patients adhere to the intervention while remaining in the state and only stop when they move to a different scenario. By dividing the healthy patients between groups, the complexity of the model is increased, but this would be relevant in RCT studies.



A



B

Figure 18: Markov models for CHD developed in similar studies. A. From Gandhi *et al.*, "Cost-effectiveness of rosuvastatin in comparison with generic atorvastatin and simvastatin in a swedish population at high risk of cardiovascular events", [124]; B. From De Vries *et al.,* "Cost-effectiveness of statins for primary prevention in patients newly diagnosed with type 2 diabetes in the Netherlands.", [29]

The complexity of the models was indicated by the number of states used within the simulation. Initial inspection tends to indicate that Figure 18B is rendered highly complex by utilising ten model states. However, this is misleading since both CHD and stroke are added to the model as disease routes. Only six of the states are related to CHD and therefore the stroke related states are not considered in this comparison.

Myopathy and *rhabdomyolysis,* adverse effects of taking statins, are only used by De Vries *et al.* and do not form part of the other models. Adverse effects were explicitly modelled in the study as additional states. These effects were added to the simulation due to the increased prevalence thereof in patients with type 2 diabetes [29], [183]. Adverse effects are excluded from Figure 9, but accounted for in the quality adjustments of the applicable states. A single model with adverse effects for all 13 interventions would reduce the simplicity of the outcomes.

Gandhi *et al.* [124] simplified their design by removing the *CHD* state from their model. CHD events are portrayed by the transition state between *initial CVD prevention* and *subsequent CVD prevention*. This differs from the other two models in which such events are an explicit

state in the design. However, all three models account for the disutility and costs of a CHD event. Patients in the three models move to a post-event state if the event was non-fatal.

In the post-event states the patients are presumed to be healthy and will continue with the simulation. Secondary prevention was not added to the *post-CHD* state for Figure 18B, since the study focussed on the effect of primary prevention. Figure 9 and Figure 18A include interventions as secondary prevention measures. In these models the possibility exists to experience an additional incident.

Additional CHD events can occur for patients in the *post-CHD* state of Figure 9 and Figure 18A. In Figure 9 the patient is able to enter the *post-CHD* state and remain alive after the additional incident, unlike in Figure 18A. It was assumed that all patients could only survive one CHD incident and would therefore die if an additional incident occurred. This assumption is not added to Figure 9, since the CHD event is represented by an individual state and not embedded in the transition states.

The termination state of all three models is *death* and can be either CHD or non-CHD related. All causes of death will move the patient to the death state, with the exception of CHD related deaths in Figure 18B. Patients experiencing a fatal CHD incident are absorbed in a separate model state, providing information on the number of CHD related fatalities and not only a combined fatality number. The number of CHD related fatalities averted was analysed by De Vries *et al.* [29], but not in the remaining two models. Therefore the designs are different, even though all three end in a state representing death.

Similarities and difference were found between the three models and illustrated the simulation process used in each. The relevance of the model in this study was identified by referring to the models developed by Gandhi *et al.* [124] and De Vries *et al.* [29]. Fundamental elements showed that this model applies a similar process to obtain relevant outcomes. This allowed the model to be used for simulating individuals and establishing a status quo of their CHD survivability.

3.4 Status quo evaluation

The individual and simulation models were described in the previous sections and a reference point was established. But the reference point for each of the two case studies was different, since several parameters were not the same. These parameters, such as biomarkers and interventions, were responsible for the main differences between the patient-specific status quos. Patient-specific base cases were developed and were evaluated in this section.

One of the initial differences was the *personal relative risk* (PRR) for the two patients. This stemmed forth out of the different biomarkers that were identified in section 3.1. In case study 1, three biomarkers (insulin, Triglycerides and HDL) were identified and a PRR of 1.13 was established for the patient. A PRR of 1.17 was calculated for the patient in case study 2, based on the LDL, CRP and HDL biomarkers that were identified. This showed that the probability for CHD was slightly higher for the patient in case study 2 and would affect his survivability.

The survivability of the patients was different through the course of the simulations. These differences were illustrated with the survival curve for each case study. Figure 19 and Figure 20 show these curves as well as the distribution between the different model states. The distributions between the models indicated how the cohort moved through the model with every simulation cycle. The distribution predicted the probability that the patient would be present within a specific model state.

The distribution was first assessed at five cycles into the simulation. This distribution represented the five-year risk of the patient and what the chances of death were. At five years, the risk of a living individual experiencing a CHD incident in case study 1 was around 9%. From the initial cohort 19% of those who had survived an incident were in the *post-CHD* state. Chances of remaining healthy or dying during the same period were 36% and 40% respectively.

Case study 2 had a distribution of 26% and 55% between the *healthy* and *death* states. The rate of dying was significantly higher due to the increased probability of dying of non-CHD related causes. Another reason for the different distributions was the higher probability of 10% for experiencing a CHD incident while still alive. At five years, 13% of the cohort had experienced a CHD incident and remained alive in the *post-CHD* state.

The different risks for CHD at five years, were consistent with the risk described by the Framingham heart study. The average 10-year risk for individuals at the age of 50 and 60 were 5% and 12% [197]. Correlation between the sets of risk values indicated that the figures were a representation of probable survivability for CHD.

Life expectancy (LE) for the cohorts was in the region of 8.00 and 4.83 years per patient. The cohort in case study 1 had a higher LE, due to the difference in initial age of the cohorts. Similarly, the QALYs for case study 2 (4.84 years) were lower compared to case study 1 (6.41 years). This difference was a continuation of the influence by the initial age parameter. LE was adjusted based on the quality of life in the model states and discounted to calculate the QALY.

Both these values were used as a reference point when interventions were added to the simulation.

The status quo was verified as a reasonable reference point for the study with Monte Carlo simulations. Monte Carlo simulations provided a population of cohorts with different characteristics which were statistically analysed. These results are given in Figure 15.

Table 15: Monte Carlo results for status quo simulations

Statistical element	Case study 1 (QALY)	Case study 2 (QALY)
Mean	6.41	4.84
Median	6.41	4.84
Minimum	5.65	4.36
Maximum	7.22	5.33
Standard deviation	0.20	0.11
95% Confidence interval	6.02 – 6.79	4.61 – 5.05

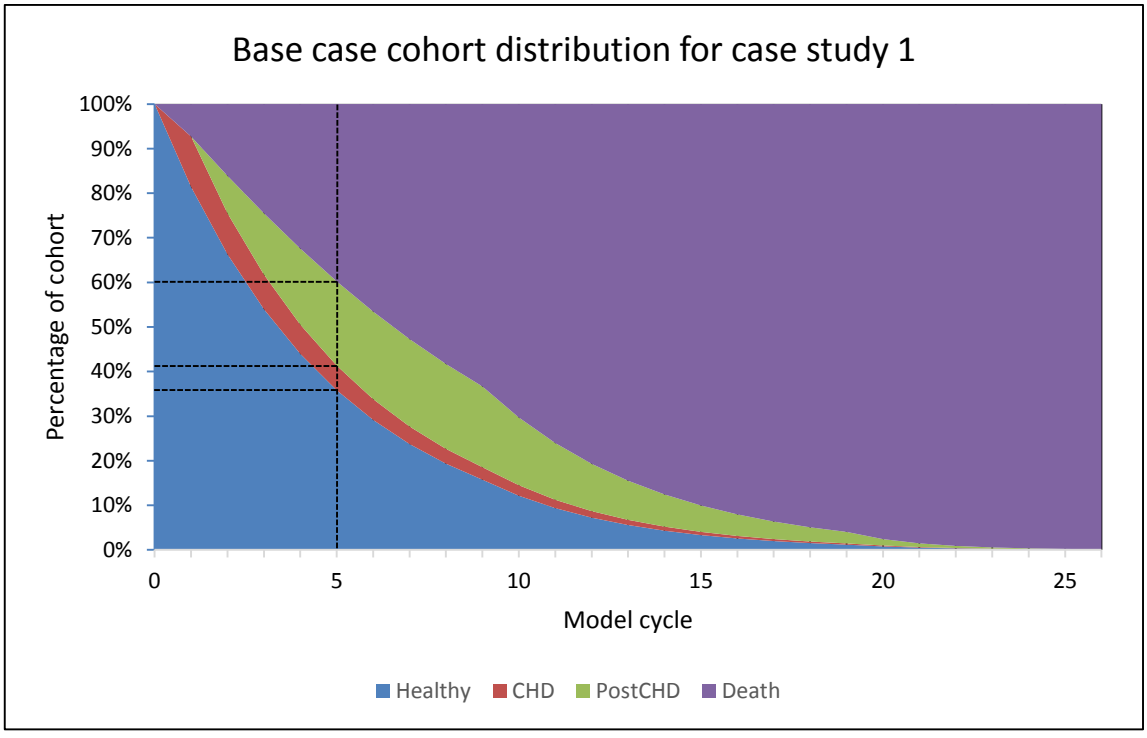


Figure 19: Survival curve of cohort without interventions for case study 1

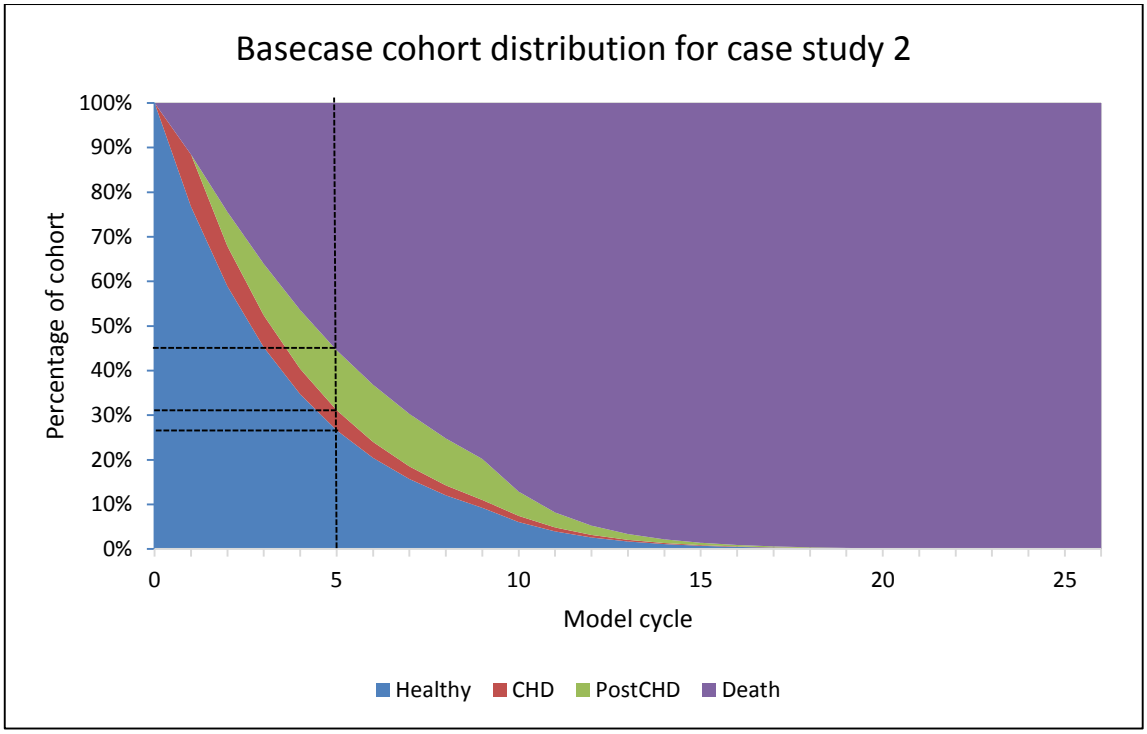


Figure 20: Survival curve of cohort without interventions for case study 2

It was found that the results indicated a significant correlation with the status quo simulation. The Monte Carlo population consisted of 10 000 simulations and yielded results similar to the status quo. The mean and median were 0.1% and 0.2% higher than their respective status quo QALY. Similarly the standard deviations for the case studies were 3.1% and 2.5% respectively. These results indicated that the model was consistent and would yield reliable outcomes for a single cohort simulation [198].

The status quo was established for both case studies and verified to ensure reliable results. Two different references were generated for analyses of continued simulations. Interventions were added to the simulation in the following section. Results for these simulations were evaluated with the status quos to determine the net effect of the interventions on the outcomes.

3.5 Simulation results for interventions

The main purpose of this study was to identify cost-effective interventions for an individual. Up to this point the model was used to generate status quos for the case studies. In this section, interventions were added to the model and comparisons with the status quo were made. The effect of an intervention was quantified based on the results that were obtained.

Interventions were added to the simulation as described in section 2.5. Each intervention was modelled separately to obtain separate effectiveness results. The interventions changed the QALY outcome values of the simulations. Figure 21 shows the QALY results for each of the interventions that were simulated in case study 1.

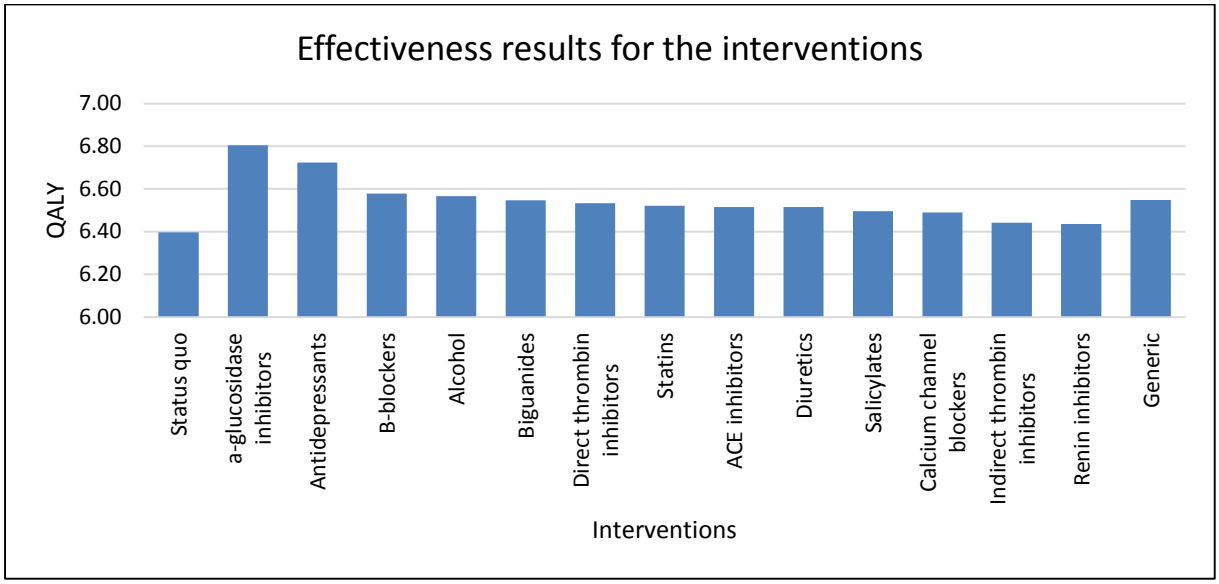


Figure 21: Effectiveness results of the interventions - case study 1

The QALY for all the interventions were higher than the results for the status quo. This indicated that all of the interventions were effective in preventing CHD to some extent. α-glucosidase inhibitors were the most effective with a QALY increase of 6%. The lowest effectiveness was seen for renin inhibitors which increased the QALY by 0.04 years. The generic intervention, which is based on the average values of all the interventions, increased the QALYs as well.

The results for case study 1 showed that all the interventions had a CHD preventative effect. Similar results were found when the interventions were added to case study 2. These results are shown in Figure 22. As in case study 1, all the interventions had a positive effect on the QALY results.

The highest effectiveness was obtained from antidepressants, increasing the QALY by 0.26 years. Statins were the least effective with an increase of 1.78%, while the generic intervention remained effective. Effectiveness results ranked differently between case study 1 and 2, due to the differing base values in the two cases. Even with these differences, the survivability of the patients were higher as a result of the preventative measures.

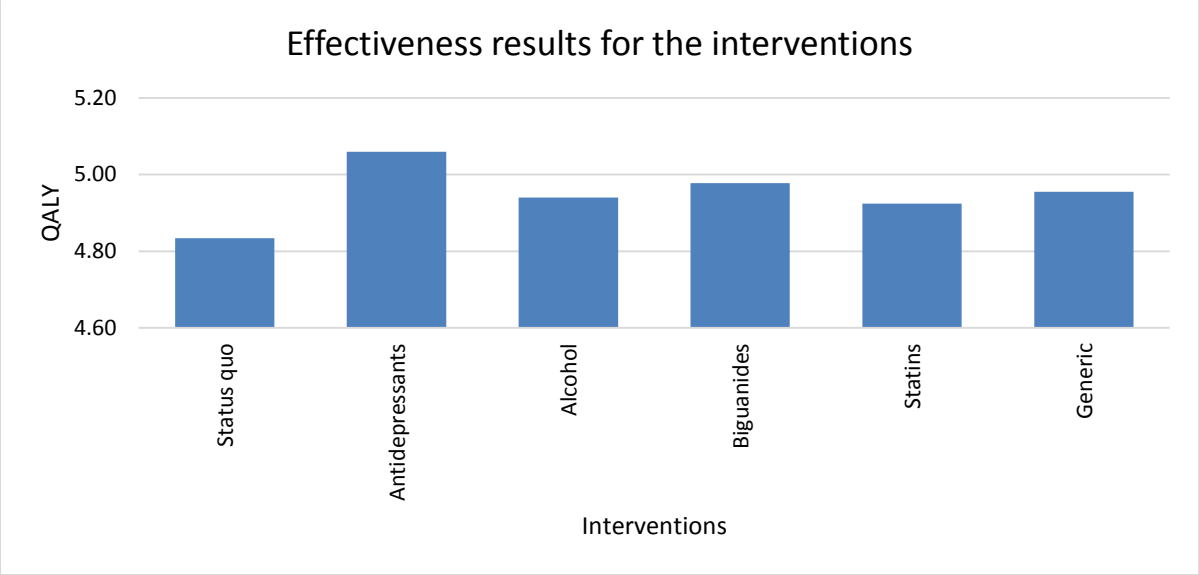


Figure 22: Effectiveness results of the interventions - case study 2

The survivability curves of the simulations with the most effective intervention (α-glucosidase inhibitors and antidepressants) are shown in Figure 23 and Figure 24. These curves were analysed after five model cycles as with status quo. Both of the curves showed a decrease in the number of the cohort distributed between the *CHD* and *post-CHD* states. The percentage of the cohort in the *death* state decreased, but by a less substantial margin.

From the curves it is evident that a larger percentage remain in the *healthy* state throughout these simulations. By using α-glucosidase inhibitors, the percentage in the *healthy* state increased by 8% and 6% for the respective case studies, while the distribution in the *death* state decreased by a mere 2.3% and 2.2% for case study 1 and 2 respectively.

These changes indicated that the intervention effectiveness was related to the number of CHD incidents. The cohort was less likely to experience a CHD incident when taking the intervention. They remained healthy for a longer period in the simulation and this is reflected by the increase in QALY.

As with the status quos, Monte Carlo simulations were performed on the simulations for both case studies. The aggregated deviation between the cohort and Monte Carlo simulations was 0.18% and 0.04%. This indicated that the results from the cohort simulations were accurate and probable within a population with differential characteristics.

Results obtained in this section indicated which interventions had the best effectiveness towards CHD. These results indicated that α-glucosidase inhibitors and antidepressants had the highest effectiveness for the case studies. However, these interventions were not

necessarily recommended due to the associated costs. The influence of costs on the recommended interventions is described and analysed in the following section

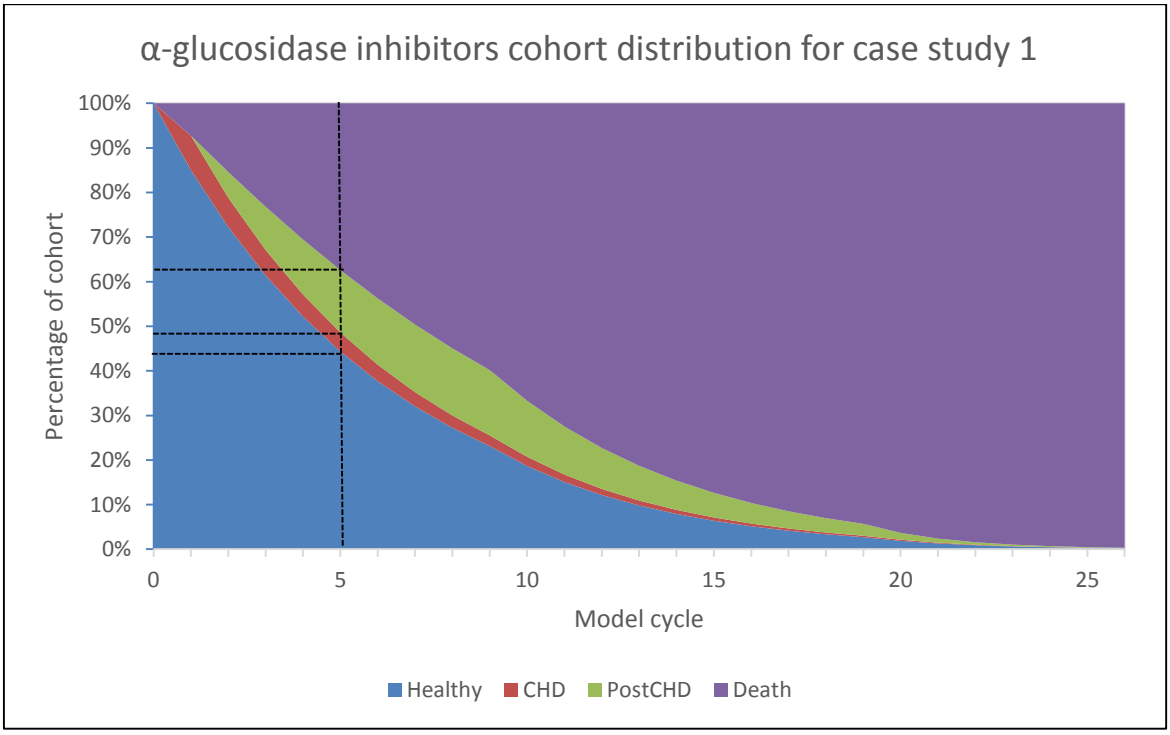


Figure 23: Survival curve of the cohort with α-glucosidase inhibitors for case study 1

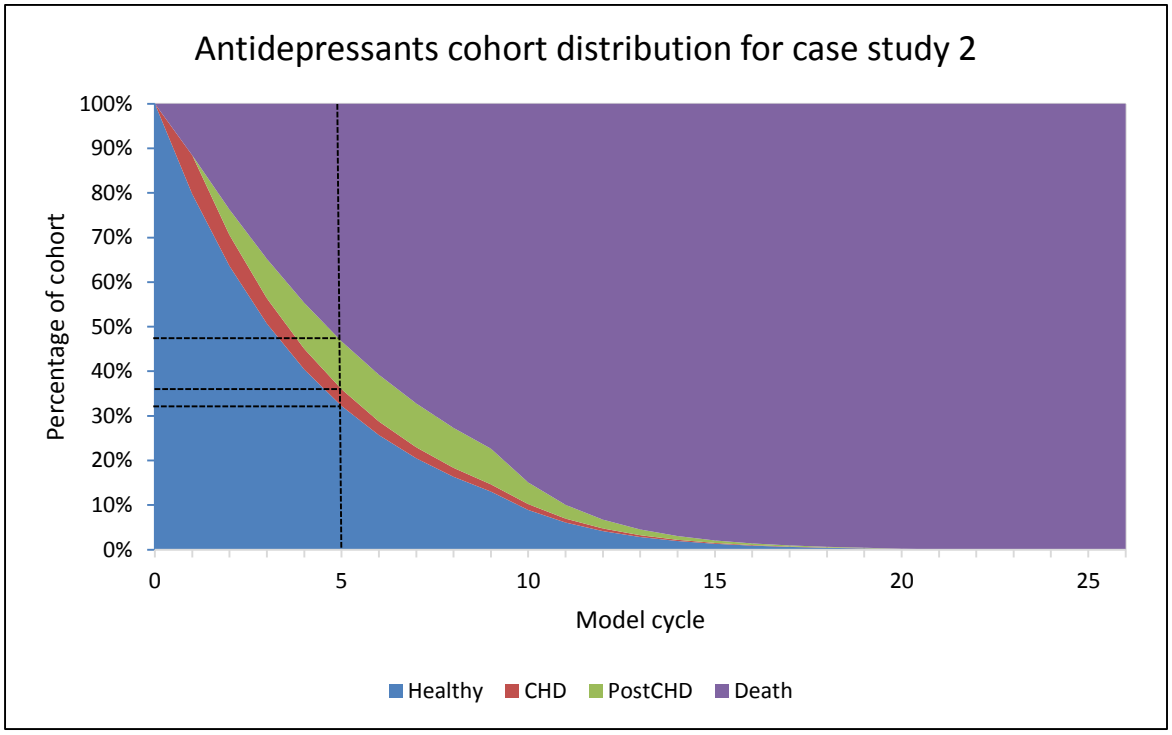


Figure 24: Survival curve of the cohort with antidepressants for case study 2

3.6 Cost-effectiveness analysis

The fiscal impact of preventative strategies is a determining factor for the decisions that are made. Highly effective interventions are often expensive, while the less expensive interventions are regarded as ineffective. In this section the cost-effectiveness of the interventions were identified and evaluated. Final recommendations were based on the outcomes of this and the previous sections.

Costs for the status quos were responsible for the base costs throughout the study. These cost were calculated from the costs of being in a specified model state. The costs of the different states were determined by the cohort distribution between them. Cost distribution between the different states for the case studies is shown in Figure 25 and Figure 26.

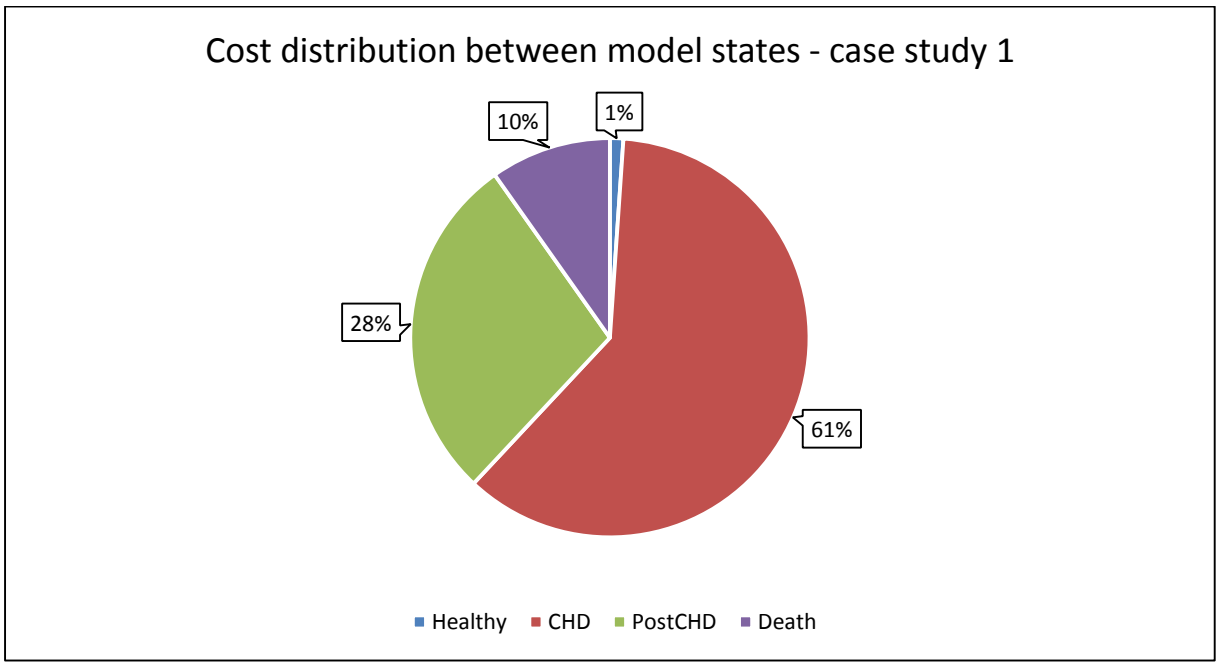


Figure 25: Cost distribution between the model states for the status quo – case study 1

Costs associated with experiencing a CHD incident were in both cases the major contributor, More than 60% of the costs were from the *CHD* state. This was a reflection of the fiscal burden that is placed on an individual when experiencing a CHD event. The effect of a lower relative risk can be seen between the two case studies.

In case study 2, the relative risk for CHD was higher and the effect on general costs is demonstrated. The higher probability of CHD is also reflected in the costs of the *post-CHD* and *death* states. A smaller proportion of the cohort were exposed to the costs of *post-CHD* and decreased the contribution to the costs. The *death* state's contribution increased due to the increase in the number of deaths by non-CHD related deaths. With lower CHD incidents a lower number of the cohort would die of the disease.

Costs for the status quo of the case studies were Int$ 35 520 and Int$ 25 088 respectively. Interventions costs were added to the case studies and the costs for following an intervention were determined. These costs are shown in Figure 27 for case study 1 and in Figure 28 for case study 2. These figures indicated that the effectiveness and intervention costs had a great influence on the expenses.

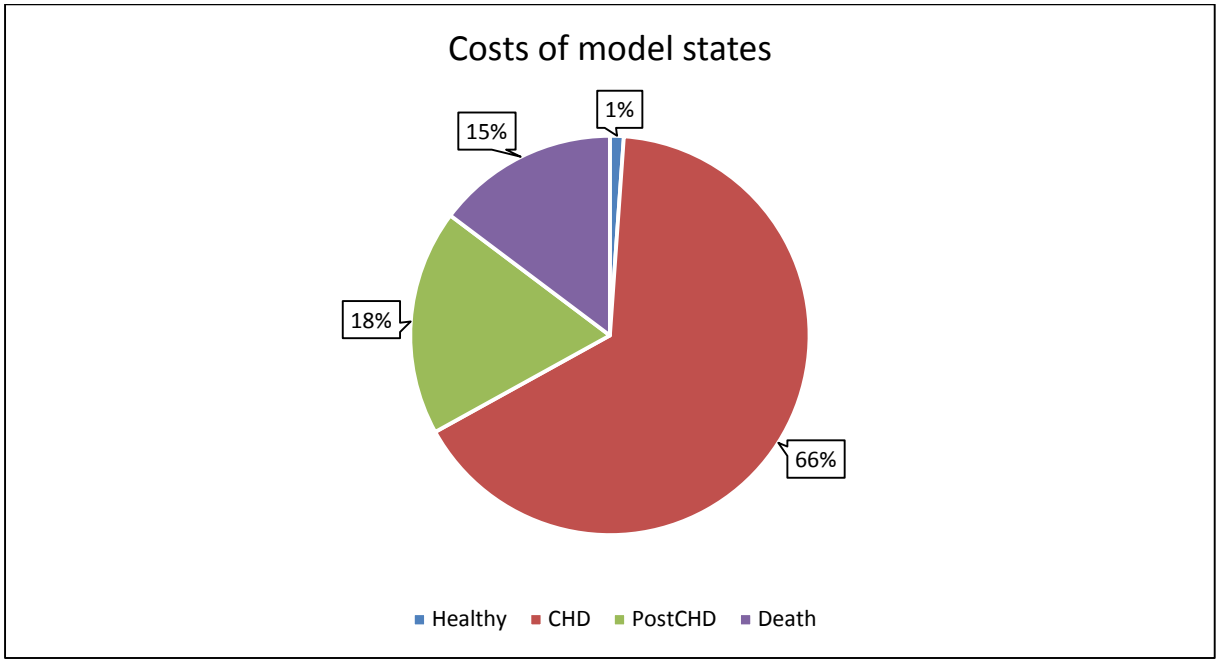


Figure 26: Cost distribution between the model states for the status quo - case study 2

Six out of the 13 interventions in case study 1 decreased the required expenditure compared to the status quo. The biggest cost decrease was observed for the β-blockers with 5% reduction. Conversely direct thrombin inhibitors were the most costly intervention. Approximately Int$ 12 700 was added to the status quo's cost. Mild alcohol consumption and calcium channel blockers were also responsible for large increases to the costs.

The average costs for case study 2 were lower than in case study 1. Alcohol resulted in a Int$ 3 300 increase, while biguanides decreased the cost by Int$ 1 800. These differential margins are lower and the spread between the results is smaller in case study 2.

Several interventions were found to be more costly while others were less expensive than the status quo. These costs were not used as the principle reason for deciding on what interventions should be recommended. The combination between the effectiveness and costs of each intervention ultimately determines the cost-effectiveness thereof.

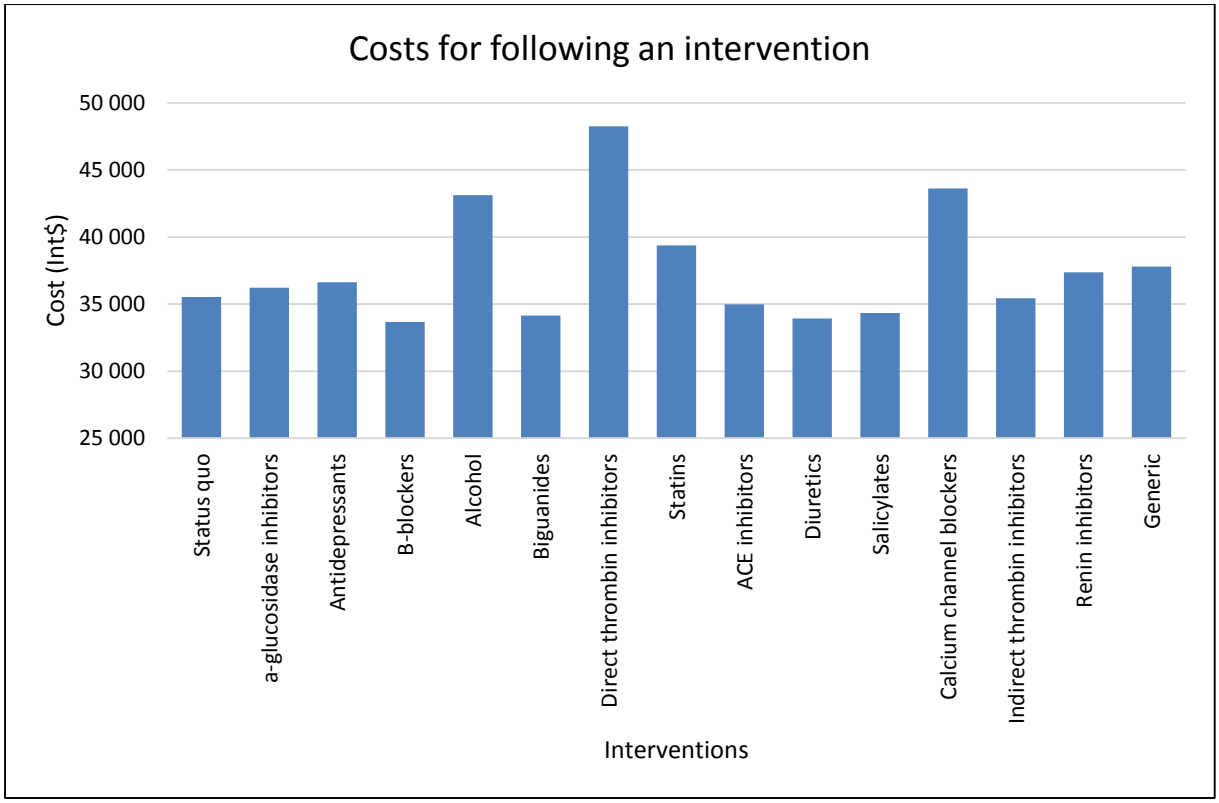


Figure 27: Intervention cost results for the simulation - case study 1

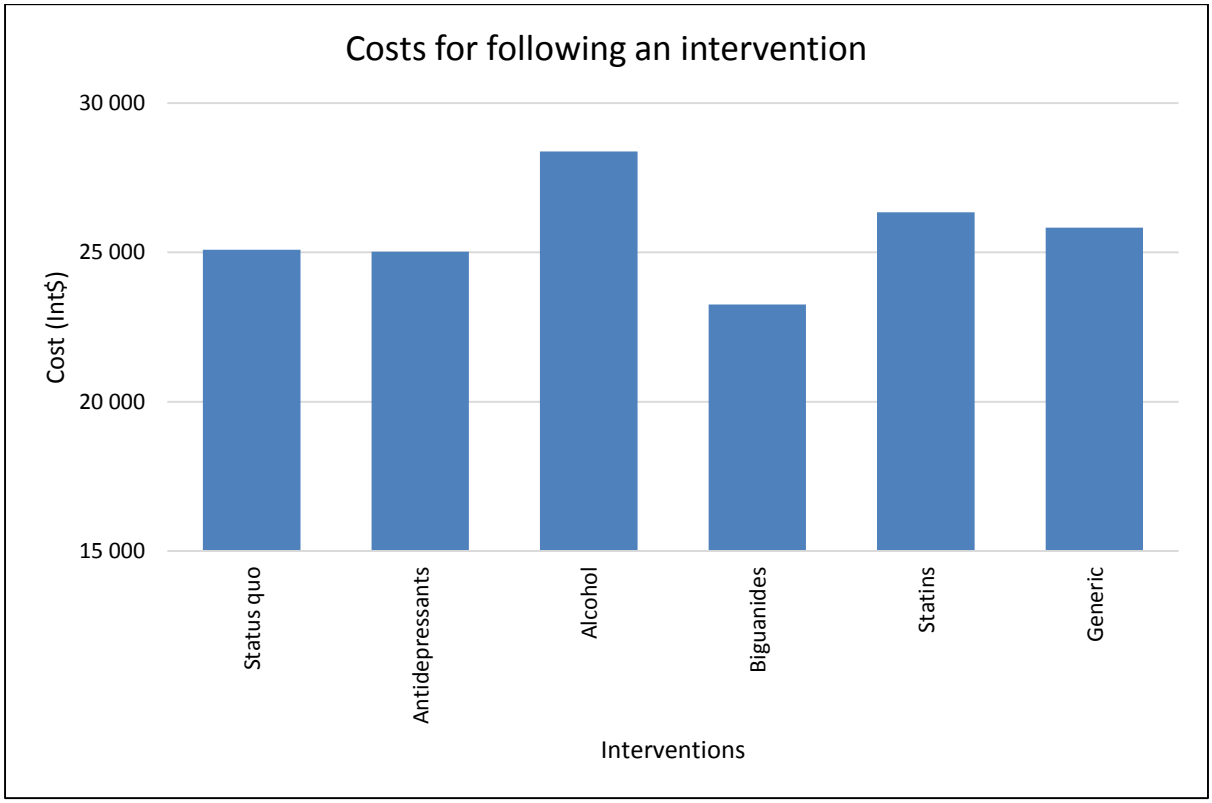


Figure 28: Intervention cost results for the simulation - case study 2

Cost-effectiveness combines the results to generate a comparable outcome. This was used to deliver a recommendation regarding interventions that could be followed. Cost-effectiveness of the interventions indicate what the benefit of one QALY would cost. The outcomes of the simulations are displayed in Figure 29 and Figure 30.

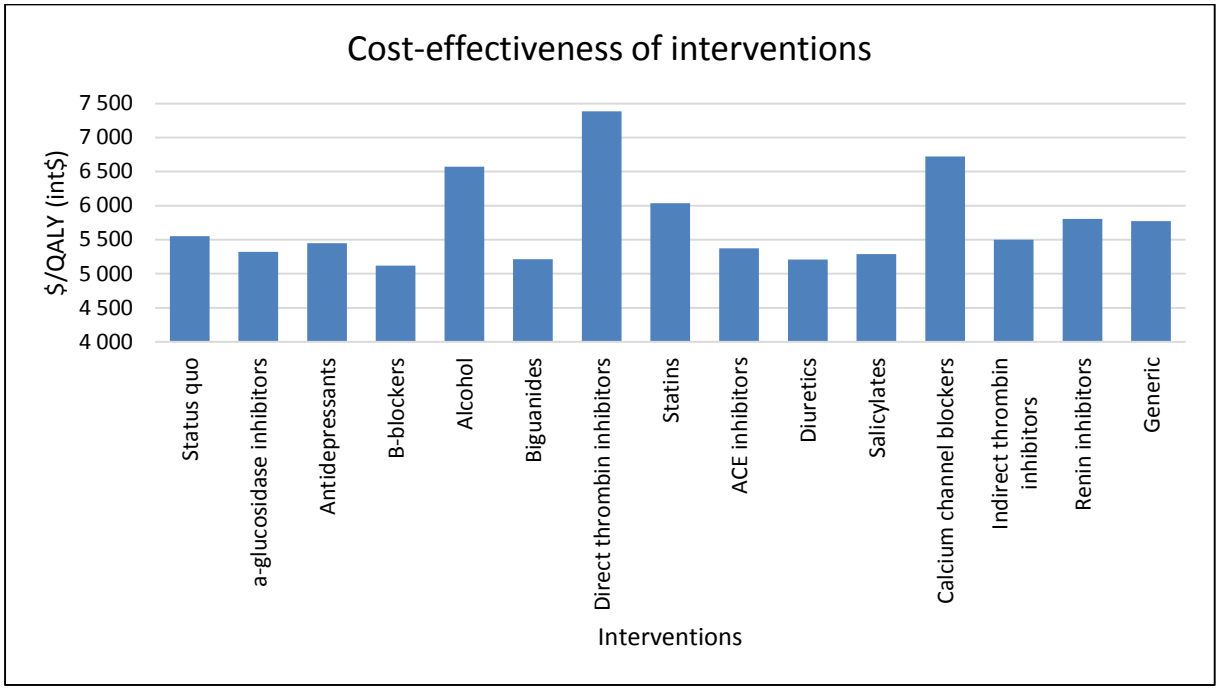


Figure 29: Cost-effectiveness of each intervention - case study 1

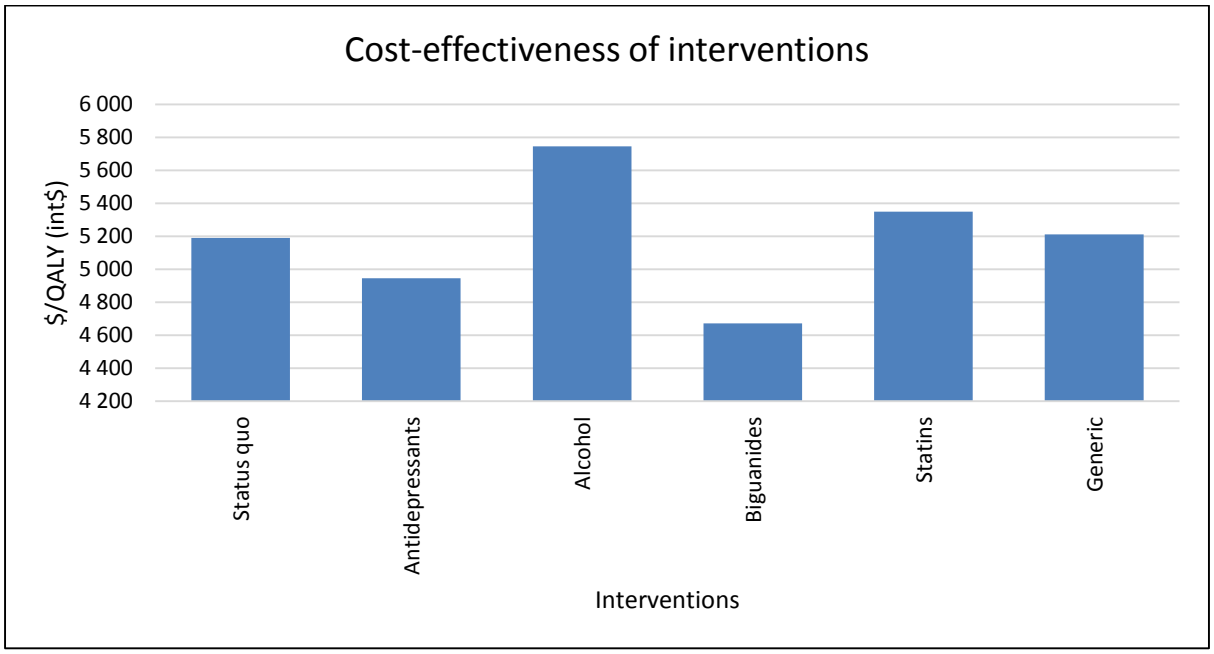


Figure 30: Cost-effectiveness of each intervention - case study 2

Several interventions were highly cost effective compared to the status quo. These were almost the same for both of the case studies. In case study 1 β-blockers were the most cost-effective and biguanides in case study 2 as these interventions required the lowest monetary input to obtain one additional QALY.

Mild alcohol consumption regarded as one of the least cost effective options in both cases. Only direct thrombin inhibitors and calcium channel blocker were less cost-effective in case study 1. These outcomes can be traced back to the unit cost of these interventions. A reduction in unit costs would allow these interventions to become competitive with other options.

Based on these outcomes the top three interventions were recommended for the case studies. These recommendations are shown in Table 16. It should be noted that these recommendations were made on the assumption that the interventions were applicable to the respective case study.

Table 16: Recommended cost-effective interventions

Case study 1	Case study 2
1. β-blockers	1. Biguanides
2. Diuretics	2. Antidepressants
3. Biguanides	3. Statins

Through the Monte Carlo simulations these values were verified to be valid. The costs of the interventions deviated from the Monte Carlo simulation by 0.47% and 1.40%, for case study 1 and 2 respectively. The cost-effectiveness results had a 0.39% and 1.44% deviation between the simulated and Monte Carlo results. These deviations indicated a high level of confidence that the results were plausible given the prevailing circumstances.

3.7 Sensitivity analysis

Critical evaluation of the effect variables have on the outcome is required to ensure the correctness of the model. Parameters related to the aim of the study should have the main influences on outcome. The effect of additional parameters should be as low as possible and not the main contributor to the outcome.

Results from the one-way sensitivity show the influence of the variables on cost-effectiveness. Variables in Figure 31 were analysed for their low and high value as specified in Chapter 2. The results indicate a range in which the results would fall if the only variable was the changed

one. A wide spread indicates a big influence as small changes would probably result in a greater variety in the outcomes.

The most significant parameters are the cost for the CHD state (*cCHD*) and the personal relative risk (*PRR*) variables. The range of these parameters are the biggest, at greater than Int$ 700 to either side of the Int$ 5 771 reference value. The biggest change is a decrease of Int$ 1 060 for the low value of *PRR*. Conversely the high value of *cCHD* (Int$ 4 860 – 6 693) results in the biggest increase.

The magnitude of the influence of these variables stresses the relevance of the survival model. *cCHD* is directly related to CHD since it is the cost for experiencing an event. By averting events, costs are reduced and the cost-effectiveness would increase. Event associated costs are the highest cost used in the model. From the sensitivity analysis it can be seen that it is more beneficial if events are averted, since the relevant costs would then be kept to a minimum.

Individual specific results are generated via the *PRR* variable. The large influence of this parameter indicates that the model is dependent on the patient's information. Individual-centred results are generated and highlights the effect of the individual's health on the model. As with the *cCHD* is it beneficial to keep the number of incidents to a minimum. An increase in the PRR will increase the probability of CHD events and would therefore in all probability increase the costs. A healthy person with a low *PRR* is more likely to experience a better cost-effectiveness benefit from interventions.

The bulk of the model is established by several parameters and not only the abovementioned variables. Interventions with moderate influence create a robust model and reduce the number of outlier results. Six of the variables are in this moderate range and support the model.

Moderate influences change the outcome between Int$ 100- 500 on either side. The average changes of these variables are Int$ 250 and Int$ 260 for the low and high values respectively. For this group, costs for the *post-CHD* model state (*cPCHD*) influence the outcome the most and the cost of dying (*cDeath*) influences it the least.

Post-CHD costs are higher compared to being healthy due to increased medical supervision. The increased costs reflect in the sensitivity analysis, however the influence is limited. As with the *healthy* state the *post-CHD* state is relatively stable and this ensures that large spikes in costs are prevented. This trend is also visible in the *cDeath* variable. This adds to the robustness of the model by reducing radical effects.

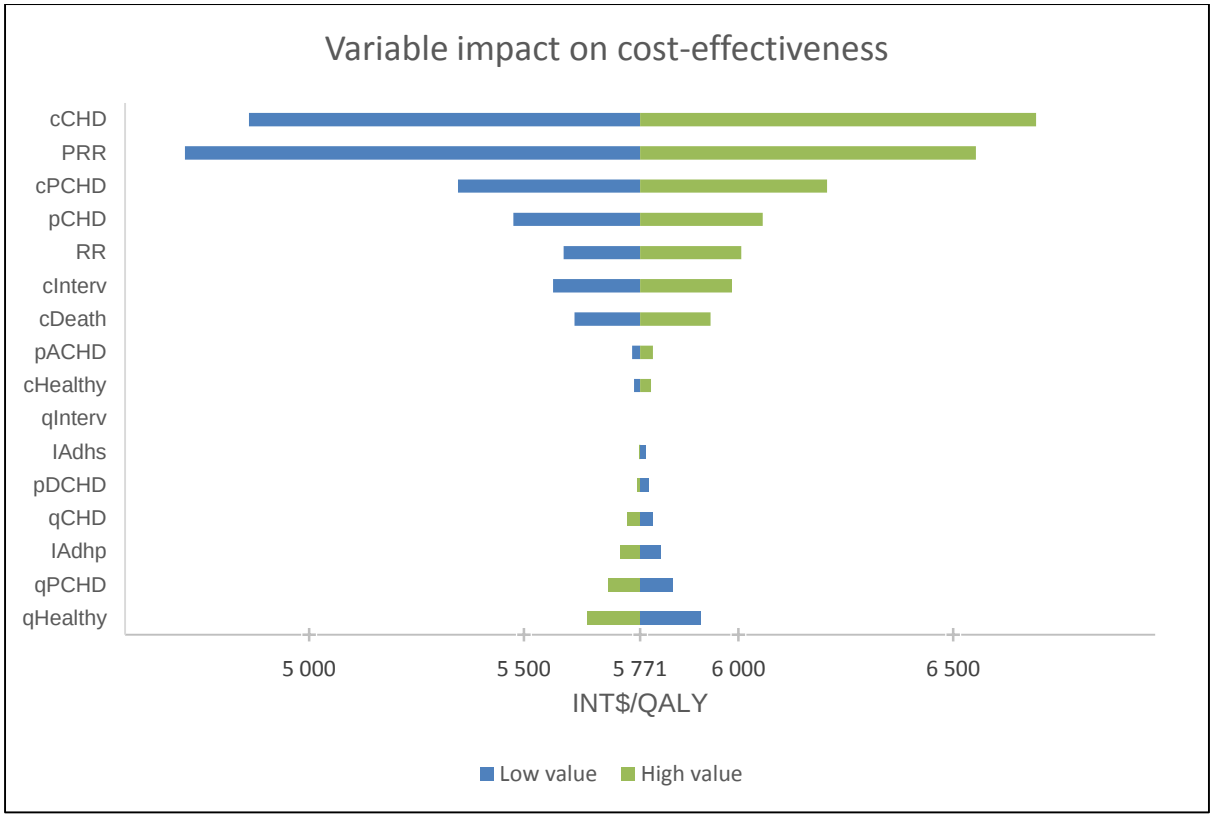


Figure 31: Tornado diagram for one-way sensitivity analysis

Probability of CHD (*pCHD*) is, contrary to expectation only a moderately influential parameter. Defined as the average probability for any individual experiencing a CHD event, it is expected that this should have a high impact. This impact is however addressed by the *PRR* variable. The design of the model focusses on the individual and therefore *pCHD* is only a base variable and not required as part of the main group.

Costs for following an intervention (*cInterv*) are low in comparison to costs of the states. Initial introduction of drugs focuses on low costs to increase the availability thereof. Cost invasion is kept to a minimum and therefore limits the impact on the model. The sensitivity range for the intervention's relative risk (*RR*) and *cInterv* are relatively similar. This allow intervention choices to be made based on either the cost and/or the relative risk of the intervention

Five of the parameters have a negligible effect on the outcome of the model. These parameters point to an overdesign and could in all probability be left out in a simplified model. However, they remain important to ensure that the model remains robust and stable. These variables form the foundation for the status quo and reference values. They also prevent situations where parameters could counter-act one another by having a reverse relation to the model.

A group of variables has a reverse correlation with the outcome costs. These are shown at the bottom of Figure 31 (*IAdhs – qHealthy*). Increases in the parameter value resulted in a decrease in costs and *vice versa.* The quality of life variables for the model states are included in this group.

Increasing the quality of a particular state decreases the costs of sustaining a high living quality. A higher quality of life can also be associated with increased health and would require lower costs to reach perfect health. The same deduction can be made for the primary and secondary adherence rates (*IAdhp* & *IAdhs*). Increased adherence would raise the general health level of the patient and therefore require fewer additional costs.

Additional costs on top of normal costs would reduce the willingness of an individual to pay for an intervention. It is therefore important to keep the additional costs along with the base costs to a minimum. Cost-effectiveness can further be described by the willingness of an individual to pay for the intervention. The generic intervention was analysed and represents all the interventions in the model. Conclusions are made on the other interventions by indicating the willingness of a population to pay for the generic option.

The probability of a population accepting the cost-effectiveness of the generic intervention is shown in Figure 32. ICER results from the probabilistic sensitivity analysis were analysed to construct a cost-effectiveness acceptability curve. Figure 32 indicates what the probability is that results would be below a specified ICER. South Africa's GDP per-capita (Int$ 13 046) is used to determine the ICER threshold for this analysis. As stated in Chapter 2, interventions are cost-effective with an ICER lower than three times the GDP per-capita.

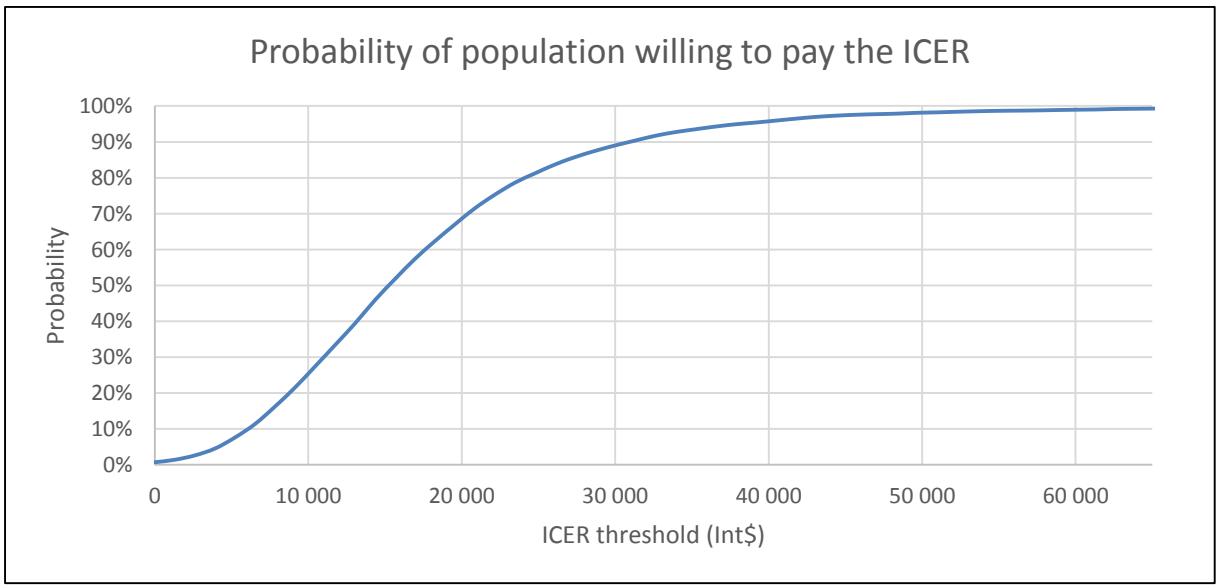


Figure 32: Cost-effectiveness acceptability curve for the interventions

Results from the analysis indicate a high probability that the generic intervention would be cost-effective. 95% of the results were below the three times GDP per-capita ICER threshold of Int$ 39 000. This shows that the generic intervention will be cost-effective for most scenarios and the population will be willing to pay the associated costs. It also indicates that several of the interventions are expected to be cost-effective, due to the composition of the generic treatment. This corresponds with the results as found in section 3.6, which show that 62% of the interventions are cost-effective.

The high cost-effectiveness of some interventions is portrayed by the fact that 40% of the results are below one GDP per-capita value. This probability shows that there are several interventions which would be classified as highly cost-effective. The slope between Int$ 5 000 – 20 000 indicates the bulk distribution of the results and most dense distribution. Therefore it can be concluded that the interventions would on average be within this acceptability range.

Analysis for the acceptability of the cost-effectiveness shows that the results are suitable for patient-specific recommendations. Costs are well accepted and in a range where an individual would be able to pay the costs if required to do so. Additional funding for the individual is not needed to support the bulk of the interventions and would be a feasible option. Recommendations from the results are feasible options which an individual or medical professional can consider as possible preventative measures.

3.8 Summary

In this chapter the method developed in Chapter 2 was applied to two case studies. Biomarkers and interventions were identified from blood tests to establish personalised characteristic models. These models were simulated to obtain a reference value for the interventions that were analysed. From the simulations the effectiveness and costs were calculated to generate cost-effectiveness comparisons between the interventions. Three interventions were recommended based, on the cost-effectiveness, as possible preventative measures for CHD. A one-way and probabilistic sensitivity analysis were performed in the end to establish the effect of each parameter on the simulation.

CHAPTER 4 – CONCLUSION AND RECOMMENDATIONS

4 Conclusion and recommendations

4.1 Conclusion

Coronary heart disease (CHD) is the leading cause of death by non-communicable diseases. Preventative efforts are dented by the failure to fully understand CHD and related causes. Several risk prediction methods were developed to account for increasing diagnosis and awareness among the world population. One such model was developed by measuring biomarkers and following the pathogenesis of the hallmark symptoms of CHD [16]. This model enables the development of patient-specific cost-effective intervention strategies based on biomarker values.

Repercussions of the worldwide financial recession in 2007 increased the fiscal burden placed on an individual with CHD. Governmental funding decreased, while the personal and private contributions to the health sector increased over the past few years. The burden placed on an individual would be reduced by prescribing cost-effective preventative interventions. A cost-effectiveness analysis in conjunction with a risk predictive model allowed identification of such preventative strategies.

Personalisation of the strategies was accomplished by combining the biomarkers of a patient to specific interventions. Biomarkers with a significant influence on the relative risk for CHD were identified through blood tests. These were further analysed by means of a risk predictive model to identify a personalised relative risk and interventions influencing the biomarkers. The influence of these parameters on survivability were established by using a simulation model.

A Markov model was developed with four main states representing the stages of CHD. A healthy cohort followed several pathways through the *CHD* and *post-CHD* states and was absorbed in the *death* state. Distribution between the states at a certain simulation cycle indicated the probability of the cohort being in that state. Monte Carlo simulations were performed in parallel with the cohort simulation. These simulations were implemented to verify the results and ensure reliable model outcomes.

Simulations consisted of two components for achieving the desired outcomes. A reference case was established before interventions were added to the simulations. Status quos were developed for two case studies and used as reference values. Differences were found between the reference values, based on variations between the model parameters. Further simulations included the interventions with probable preventative effects.

Interventions were added to the model simulations to establish their effectiveness. These simulations indicated that all the interventions had a preventative effect with regards to CHD. This improved the survivability of the cohorts by averting CHD incidents. The results were verified through Monte Carlo simulations that were performed on all the interventions. Highly effective interventions were identified, but recommendations were withheld until after the completion of the cost analysis.

Present and past CHD incidents contributed the most to the costs distribution within the model states. The costs for following an intervention were influenced by the unit cost as well as the effectiveness. Prevention of CHD incidents and a low unit cost lowered the financial effect of the interventions. Most of the interventions were relatively cost-effective with a few outliers because of their unit costs. Recommendations on interventions were made after verifying the results with Monte Carlo simulations. Three cost-effective interventions were identified for each of the case studies of which one intervention was recommended for both.

One way and probabilistic sensitivity analyses were performed to quantify simulation uncertainty. A generic intervention was used to evaluate the prescription related variables. The one way analysis indicated that the two most influential variables were the cost of a CHD incident and the personal relative risk, while the probabilistic sensitivity analysis showed that most interventions would be cost-effective. Further results showed that the model was robust and allowed a genuine representation of the results.

Recommended interventions were regarded as feasible options for preventative strategies. An individual or medical professional can therefore establish a personalised cost-effective method to prevent or manage CHD.

4.2 Recommendation for further research

Limitations and results from the study left several areas open for future investigations. Studying these areas will add to the broad understanding of CHD and the cost effectiveness of the interventions.

Availability of past studies excluded health factors from the model that was used. The inclusion of health factors would allow the patient to make lifestyle modifications in order to reduce the risk for CHD. Recommended interventions will be able to include such changes along with the pharmaceutical drugs.

Influence by the adverse effects for the drugs were limit to the quality adjustments of the model states. Including additional model states for the adverse effects in the model would yield more accurate cost-effectiveness results. Costs associated with the adverse effects would be included and not accounted for based on an adjustment. Several additional studies will have to be performed to ensure that the probability and costs of these effects are well defined.

The level of making patient specific recommendations will improve with an in depth analysis of the relative risk of the individual. Relative risks associated with the biomarkers should be adjusted proportionally to the blood test results. This will give a more accurate predictions of the individual's risk. This will increase the accuracy of the study since the personal relative risk was one of the variables with the highest impact on the outcomes.

Additional case studies should be performed to ensure statistical significance of the entire procedure. Costs related to blood tests and the sensitive nature of the results limit the access to data. An increased data pool would evaluate the accuracy, consistency and the repeatability of the outcomes. The large data pool would allow small adjustments to be made for improving the accuracy.

Improved accuracy on the recommendations can be achieved with follow-up studies after implementation. Performing a follow-up study on the patients will serve as a verification if the recommendations were helpful. Based on these results can the process be streamlined and improved to ensure the most beneficial results possible.

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