M-IEM | HCTM | MASTER THESIS

# THE POTENTIAL COST-EFFECTIVENESS OF HOME-BASED SCREENING FOR THE EARLY DETECTION AND TREATMENT OF CVD, CKD, AND DM2

## A DISCRETE-EVENT SIMULATION STUDY

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# Preface

This master thesis is the final piece of work of my Master in Industrial Engineering and Management at the University of Twente. My student life started in Eindhoven at the University of Technology in 2017. After completing my Bachelor's Degree in Industrial Engineering, I went to the University of Twente to start the master of IE&M, focusing on Healthcare Technology and Management. Over the years, I have enjoyed student life in both Eindhoven and Twente. During my master's, I even had the opportunity to go a semester abroad to Lisbon, Portugal. I am very thankful for all the opportunities I have had over the past six years and the enriching student life I have been part of. I want to express my gratitude to all who have been part of this incredible journey.

In particular, I would like to thank my first University supervisor, Xavier Pouwels, for the weekly guidance and support during my master's thesis. Our sessions motivated me to explore new perspectives I haven't previously considered. Your feedback truly encouraged me to go the extra mile. I also want to thank Erik Koffijberg for dedicating time to share his valuable insights into health economics and modeling and for inspiring me to contemplate my future professional career in the healthcare sector.

This master thesis also marks the end of an incredible student life. Therefore, I also want to thank my friends in Eindhoven and Twente. Finally, I want to express my gratitude to my parents for their unconditional trust and support.

I hope you find this report insightful and enjoyable to read.

Koen van der Velden

Amsterdam, December 2023

# Executive Summary

Cardiovascular disease (CVD), chronic kidney disease (CKD), and type 2 diabetes (DM2) currently affect millions of people in the Netherlands. When these diseases are not detected and treated at an early stage, they can lead to major complications such as a stroke, myocardial infarction, cardiac arrest, and kidney failure. Such complications have a large impact on quality of life, people's participation in society, and their survival. Many people are unaware of having CVD, CKD, and DM2, as early disease stages generally do not result in apparent signs or symptoms. Therefore, they often remain undiagnosed and untreated until the disease has progressed to a more severe stage or until a (major) complication occurs. Besides the adverse health effects, CVD, CKD, and DM2 also bring significant costs to society. Approximately 9% of the total health expenditures in the Netherlands are caused by these diseases. Despite the adverse health and economic effects, there currently is no national screening approach for early detection and treatment of CVD, CKD, and DM2 for the general population of the Netherlands.

The HTSR group of the University of Twente is partnering with the Check@Home consortium. They aim to assess the feasibility, effectiveness, and cost-effectiveness of a national home-based screening program for the early detection and treatment of CVD, CKD, and DM2. The target population is the population in the Netherlands aged 50-75 years. The screening program will consist of an at-home albuminuria test, an atrial fibrillation test, and a questionnaire to detect coronary artery disease, heart failure, and type 2 diabetes. The primary objective of this master thesis was to develop a health economic model to assess the potential health economic impact of the Check@Home screening program. To evaluate the health economic impact, we compared the costs and health effects of the screening program with usual care (i.e., no screening). Consequently, the main research question of this master thesis was: "What is the expected health economic impact of a national home-based screening program for the early detection and treatment of CVD, CKD, and DM2, compared to usual care in the Netherlands?"

A non-constrained discrete-event simulation (DES) model was developed to assess several outcomes. The primary outcomes were costs, life years, and quality-adjusted life years (QALYs). The health and cost outcomes were compared incrementally, using the incremental cost-utility ratio (ICUR) against a willingness to pay threshold of €20,000 per QALY gained. Secondary outcomes were the number of new diagnoses found through screening, the number of CVD-related complications (i.e., ischemic stroke, hemorrhage stroke, myocardial infarction, cardiac arrest, and acute heart failure), the number of renal replacement therapies (RRTs), and the average time until a CVD complication or kidney failure progression occurred. We also examined the disease status at the start and end of the simulation time. The disease status indicated which disease an individual had, what disease stage they were in, and whether they were diagnosed or undiagnosed. The disease status was used to compare the stage distribution and the ratio of diagnosed-undiagnosed individuals between usual care and screening.

Multiple analyses were performed to evaluate the health and economic impact of the Check@Home screening program. First, a deterministic analysis was performed, where we compared screening with usual care at parameter means. Furthermore, a scenario analysis was performed, evaluating an optimistic and pessimistic scenario. In the two scenarios we adjusted the model inputs for participation in the screening process, costs of screening, and diagnostic performance. Finally, a probabilistic sensitivity analysis was performed to evaluate the effect of

parameter uncertainty on the health economic outcomes. All analyses were performed from a healthcare system perspective over a lifetime horizon.

Results from the deterministic analysis showed that screening, compared to usual care, resulted in lower mean costs per individual (- €25.13) and better health effects per individual (+ 0.010 QALYs and + 0.014 life years), leading to an ICUR of - €2,519.48. The ICUR implied that screening was cost-saving compared to usual care. In the total target population (5.66 million people in the Netherlands), screening saved €142,327,781, and yielded 56,491 QALYs and 73,235 life years compared to usual care. Furthermore, the screening strategy prevented 14 CVD complications per 10,000 individuals compared to usual care over the simulation lifetime (i.e., from 2830 to 2816 complications per 10,000 individuals). On average, CVD complications occurred 0.02 years later in the screening strategy than in usual care. Additionally, the screening strategy prevented 2 CKD patients from developing kidney failure per 10,000 individuals compared to usual care over the simulation lifetime (i.e., from 408 to 406 kidney failure patients per 10,000 individuals). The average time until CKD patients progressed to kidney failure increased by 0.20 years in the screening strategy. Of the kidney failure patients, fewer received RRT. Moreover, there were proportionally more patients diagnosed than undiagnosed in the screening strategy compared to the usual care strategy, implying that screening was effective in detecting diseases. On top of that, diagnosed patients were generally in less advanced disease stages in the screening strategy compared to usual care.

In an optimistic scenario (i.e., higher participation in the screening process, lower costs of screening, and higher diagnostic performance compared to the base-case scenario), screening resulted in lower mean costs per individual (- €2.20) and better health effects per individual (+ 0.021 QALYs and + 0.035 life years), leading to an ICUR of - €98.34. The ICUR implied that screening in an optimistic scenario was cost-saving compared to usual care. Compared to the base-case scenario, screening in an optimistic scenario resulted in higher costs and better health effects per individual (i.e., more life years and more QALYs). Higher costs in the optimistic scenario can be explained by more diseases being detected through screening (i.e., 4.3% in the base-case scenario and 6.6% in the optimistic scenario), resulting in more patients being treated earlier than in the base-case scenario. Better health effects in the optimistic scenario can be explained by the fact that CVD complications and progression to kidney failure occurred later than in the base-case scenario. In a pessimistic scenario (i.e., lower participation in the screening process, higher costs of screening, and lower diagnostic performance compared to the base-case scenario), screening resulted in lower costs per patient (- €5.80) and better health effects (+ 0.002 QALYs and + 0.001 life years), leading to an ICUR of -€4,488.79. The ICUR implied that screening was still cost-saving compared to usual care. However, the incremental health effects were limited. The health effects were limited because fewer diseases were detected through screening (2.7%). Hence, fewer patients were treated earlier. The number of CVD complications and the number of patients progressing to kidney failure decreased compared to usual care, but not as much as in the base-case scenario for screening.

The mean results in the probabilistic sensitivity analysis showed that screening was cost-saving compared to usual care with an ICUR of - €173.86. However, the incremental cost-effectiveness plane showed that parameter uncertainty significantly affected the health economic outcomes of the model. Furthermore, at a willingness to pay threshold of €20,000 per QALY, there was a 65.5% probability of screening being cost-effective. The question remains how stable the results from the probabilistic sensitivity analysis are, as only 200 runs were performed.

Overall, this master thesis suggests that a national home-based screening program for CVD, CKD, and DM2 in the general population of the Netherlands holds promise. The results from the deterministic analysis support the potential cost-effectiveness of screening and improved patient outcomes. However, the probabilistic sensitivity analysis acknowledges that there is uncertainty regarding outcomes of the health economic model. For future research, we recommend verifying and validating the assumptions, model inputs, and results with clinical experts to improve the model's quality, credibility, and robustness. Furthermore, we recommend extending the health economic model and analyses.

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# List of Abbreviations

| | |
|---|---|
| **ACR** | Albumin-Creatine Ratio |
| **AF** | Atrial Fibrillation |
| **aHF** | acute Heart Failure |
| **CAD** | Coronary Artery Disease |
| **CA** | Cardiac Arrest |
| **CKD** | Chronic Kidney Disease |
| **CVD** | Cardiovascular Disease |
| **DCVA** | Dutch Cardio Vascular Alliance |
| **DES** | Discrete Event Simulation |
| **DM2** | Type 2 Diabetes |
| **eGFR** | estimated Glomerular Filtration Rate |
| **ESD** | Event Specific Distribution approach |
| **ESRD** | End Stage Renal Disease |
| **GP** | General Practitioner |
| **HDL** | High-Density-Lipoprotein |
| **HF** | Heart Failure |
| **HR** | Hazard Ratio |
| **HS** | Hemorrhage Stroke |
| **HTSR** | Health Technology and Service Research |
| **ICD-10** | International Classification of Diseases – edition 10 |
| **ICER** | Incremental Cost Effectiveness Ratio |
| **ICPC** | International Classification of Primary Care |
| **ICUR** | Incremental Cost Utility Ratio |
| **IS** | Ischemic Stroke |
| **LVEF** | Left Ventricular Ejection Fraction |
| **LY** | Life Years |
| **MI** | Myocardial Infarction |
| **NHG** | Dutch General Practitioners Associations |
| **NYHA** | New York Heart Association |
| **NOW** | Dutch Organization for Scientific Research |
| **PSA** | Probabilistic Sensitivity Analysis |
| **QALY** | Quality Adjusted Life Years |
| **RR** | Relative Risk |
| **RRT** | Renal Replacement Therapy |
| **SBP** | Systolic Blood Pressure |
| **TC** | Total Cholesterol |
| **TIA** | Transient Ischemic Attack |
| **UCD** | Urine Collection Device |
| **WTP** | Willingness-To-Pay |
| **ZiN** | National Health Care Institute |

# 1. Introduction

According to the World Health Organization, cardiovascular diseases are the leading cause of death globally, taking an estimated 17.9 million lives each year. This is equal to 32% of all global deaths (WHO, 2021). In the Netherlands, cardiovascular diseases are the second leading cause of death after cancer (CBS, 2022). Cardiovascular diseases are a group of disorders of the heart and blood vessels, including coronary artery disease, heart rhythm disorders, and other heart conditions (WHO, 2021). Chronic diseases such as type 2 diabetes and chronic kidney disease increase the risk of cardiovascular disease. These chronic diseases are interrelated and share common risk factors such as hypertension (i.e., high blood pressure) and hypercholesterolemia (i.e., high cholesterol level) (Jankowski et al., 2021).

Cardiovascular disease (CVD), chronic kidney disease (CKD), and type 2 diabetes (DM2) currently affect millions of people in the Netherlands. An estimated 1.7 million people suffer from CVD in the Netherlands (Hartstichting, 2021). For CKD and DM2, this is respectively 1.7 million and 1.2 million people (Nierstichting, n.d.; Diabetes Fonds, n.d.). Due to an aging population, the number of people suffering from these diseases is expected to grow even further in the coming years (RIVM, 2018). When these diseases are not detected and treated at an early stage, they can lead to major complications such as stroke, myocardial infarction, cardiac arrest, or kidney failure. Such complications have a significant impact on people's quality of life, people's participation in society, and impact on survival (UMC Utrecht, 2022; WHO, 2021). Many people are not aware of having CVD, CKD, and DM2, as early disease stages generally do not result in apparent signs or symptoms. Therefore, these diseases often remain undiagnosed and untreated until the disease has progressed to a more severe stage or until a (major) complication occurs (Diabetes Fonds, n.d.-b; Hartstichting, n.d.-a; Nierstichting, n.d.-c).

In addition to these major adverse health effects, there is a significant negative economic effect. Within the Dutch healthcare system, CVD is the fifth most expensive disease (Volksgezondheid en Zorg, 2022b). Healthcare expenditure for CVD was 6.8 billion Euros in the Netherlands in 2019, equal to 6.9% of the total expenditure for the Dutch healthcare system. Most expenditure (65%, 4.4 billion Euros) went to hospital care and specialistic care, followed by medicines and medical devices (13%, 858 million Euros) (Volksgezondheid en Zorg, 2022a). The healthcare expenditures for CKD and diabetes (including type 1 diabetes) were respectively 805 million Euros and 1.3 billion Euros in the Netherlands in 2019 (Volksgezondheid en Zorg, 2022b). Despite the adverse health and economic impact of these diseases, there currently is no national screening program for the early detection and treatment of CVD, CKD, and DM2 for the general population of the Netherlands.

### *Check@Home*

Check@Home is an initiative of the Dutch CardioVascular Alliance (DCVA), the Heart Foundation, the Kidney Foundation, the Diabetes Fund, and several partnering universities and hospitals. The initiative is (co-)financed by the Dutch Organization for Scientific Research (NWO). Check@Home was inspired by the THOMAS study. The THOMAS study was initiated in 2019 and aimed to evaluate the cost-effectiveness of at-home screening for albuminuria (i.e., presence of the albumin protein in the urine). Preliminary results from the THOMAS study showed that the at-home albuminuria test is an easily accessible and cost-effective tool for detecting unknown CKD. Furthermore, screening for albuminuria can help to detect unknown cardiovascular risk factors,

such as (pre-) diabetes, hypertension, and hypercholesterolemia (Gansevoort, 2022; van Mil et al., 2022).

Check@Home will build further on the lessons learned in the THOMAS study. The Check@Home study aims to assess the feasibility, effectiveness, and cost-effectiveness of an at-home national screening program for the early detection and treatment of CVD, CKD, and DM2. With this, Check@Home aims to prevent progression and complications. Various stakeholders are involved in the consortium. In addition to participating citizens and patients, several healthcare professionals and research groups participate in the study. Given the substantial size of the study, Check@Home is divided into eight work packages and five disease domains. The Health Technology and Services Research (HTSR) department of the University of Twente leads work package five: "Impact on Health and Economic Outcomes". In this work package, the HTSR department will assess the expected health and economic impact of home-based screening, focusing on five disease domains: atrial fibrillation (AF), coronary artery disease (CAD), heart failure (HF), CKD, and DM2 (Check@Home, 2022).

### *Home-based Screening*

Today, general practitioners (GPs) play an essential role in identifying people with an increased risk of CVD and in determining whether these people are eligible for interventions. Current guidelines from the Dutch GPs Association (NHG) recommend screening for CVD among specific subpopulations as they visit the GP for a consultation. For example, the advice is to regularly screen men older than 40 years and women older than 50 years without known risk factors of CVD (NHG, 2019a).

To diagnose people with CVD, CKD, and DM2 earlier, Check@Home wants to explore the feasibility, effectiveness, and cost-effectiveness of a national home-based screening program. A study program was developed in four participating regions in the Netherlands (Breda, Utrecht, Arnhem, and Eindhoven). In total, 160,000 participants aged between 50-75 years living in one of the four regions will be invited to participate in the study with an at-home test using the Check@Home digital platform. The at-home test will consist of standard tests and innovative add-on tests. Standard tests include certified tests that are already implemented in practice, such as the albuminuria test from the THOMAS study. Other standard tests are the AF-test, the validated RED-CVD questionnaire for detecting CAD and HF (Groenewegen et al., 2021), and a questionnaire for detecting DM2. The AF-test consists of a CE-certified technology that screens and monitors heart rate, heart rate variability, and heart rhythm disorders by using a smartphone camera without the use of any other hardware (Check@Home, 2022; Happitech, n.d.). Examples of add-on tests are the ECG patch, HbA1c finger prick, and a glucose sensor for continued (2-week) measurement. In case of early signs of CVD, CKD, or DM2, participants are invited for extensive screening in a regional diagnostic center. If necessary, patients receive appropriate treatment, such as lifestyle advice and medication (Check@Home, 2022).

### *Problem Statement and Research Objective*

CVD, CKD, and DM2 are diseases with major adverse health and economic effects. A national home-based screening program for the early detection and treatment of CVD, CKD, and DM2 can help to prevent progression and complications. To evaluate the cost-effectiveness of a national home-based screening program, the expected impact on health and cost outcomes need to be assessed. Even though, at the moment, there is no patient data available, it is deemed relevant to evaluate the expected health economic impact. Analyzing the expected health economic impact

now helps to inform the Check@Home consortium about the potential cost-effectiveness of home-based screening in the future.

The main research objective of this master thesis is to develop a first health economic model for the HTSR group and to provide an initial understanding of the cost-effectiveness of a national one-off home-based screening program for CVD, CKD, and DM2. The first health economic model can support future model development and decisions on potentially valuable future research. To evaluate the cost-effectiveness of screening, we compare screening with usual care (i.e., current standard of care: no screening). The results of the health economic model and the comparison between the usual care and screening will be used to inform Check@Home about the potential health economic impact of screening. In addition to a base-case scenario for screening, we aim to evaluate the health economic impact of screening in an optimistic and pessimistic scenario.

### *Research Questions*

Following the problem statement and research objective, the main research question of this master thesis is: *What is the expected health economic impact of a national home-based screening program for the early detection and treatment of CVD, CKD, and DM2, compared to usual care in the Netherlands?*

Four sub-research questions support the main research question.

1. *How is the diagnostic and treatment pathway for CVD, CKD, and DM2 structured in the Netherlands?*
2. *Which model inputs do we select for constructing an optimistic and pessimistic scenario for home-based screening, and what values do we use for the selected model inputs?*
3. *What is the expected health economic impact of the optimistic and pessimistic scenario for home-based screening compared to usual care in the Netherlands?*
4. *How uncertain are the health economic outcomes and recommendations due to parameter uncertainty in the health economic model?*

### *Outline*

The remainder of this report is structured as follows: Chapter 2 presents the methodology and the health economic model. Subsequently, in Chapter 3 we analyse the impact of two major assumptions on the health economic outcomes of the model. Chapter 4 presents the results from the deterministic analysis, and Chapter 5 presents the results from the probabilistic sensitivity analysis. In Chapter 6 we discuss the main findings and research limitations and provide future research. Finally, Chapter 7 completes the report with the conclusions.

For theoretical background, we refer to the Appendix. Appendix 1 contains an elaborate description of the five disease domains, including symptoms, risk factors, complications, and diagnostic and treatment options. Furthermore, Appendix 2 describes the key concepts in health economic evaluations. In Appendix 3, we describe two types of models used in health economic evaluations (i.e., state-transition models and discrete-event simulation models). Appendix 4 provides an overview of previous health economic evaluations on population-based screening within the five disease domains.

# 2. Methodology and Health Economic Model

This Chapter describes how we developed the health economic model for Check@Home. In Section 2.1, we describe the model setting using the PICO framework. In Section 2.2, we explain which model type we choose for evaluating the health economic impact of Check@Home. Subsequently, in Section 2.3, we present the diagnostic and treatment pathway for CVD, CKD, and DM2, including the structural assumptions made. The evaluated screening strategy is described in Section 2.4. Thereafter, in Section 2.5, we describe how we defined the patient characteristics at model initiation. In Section 2.6, we explain how we modelled the events in the health economic model. The utilities and costs used in the health economic model are listed in Section 2.7 and Section 2.8, respectively. In Section 2.9, we describe how we implemented discounting on costs and effects. Finally, Section 2.10 describes the analyses performed, including the deterministic analysis and the probabilistic sensitivity analysis.

## 2.1. Setting

To understand the setting of the health economic model, Figure 1 presents a PICO framework, introducing the population, intervention, comparison, and outcomes evaluated. The population evaluated in the health economic model was the general population of the Netherlands aged 50 to 75 years. Table 1 provides a high-level overview of the baseline characteristics of the population evaluated. In Section 2.5 we elaborate on the choices made for assigning initial characteristics at model initiation.

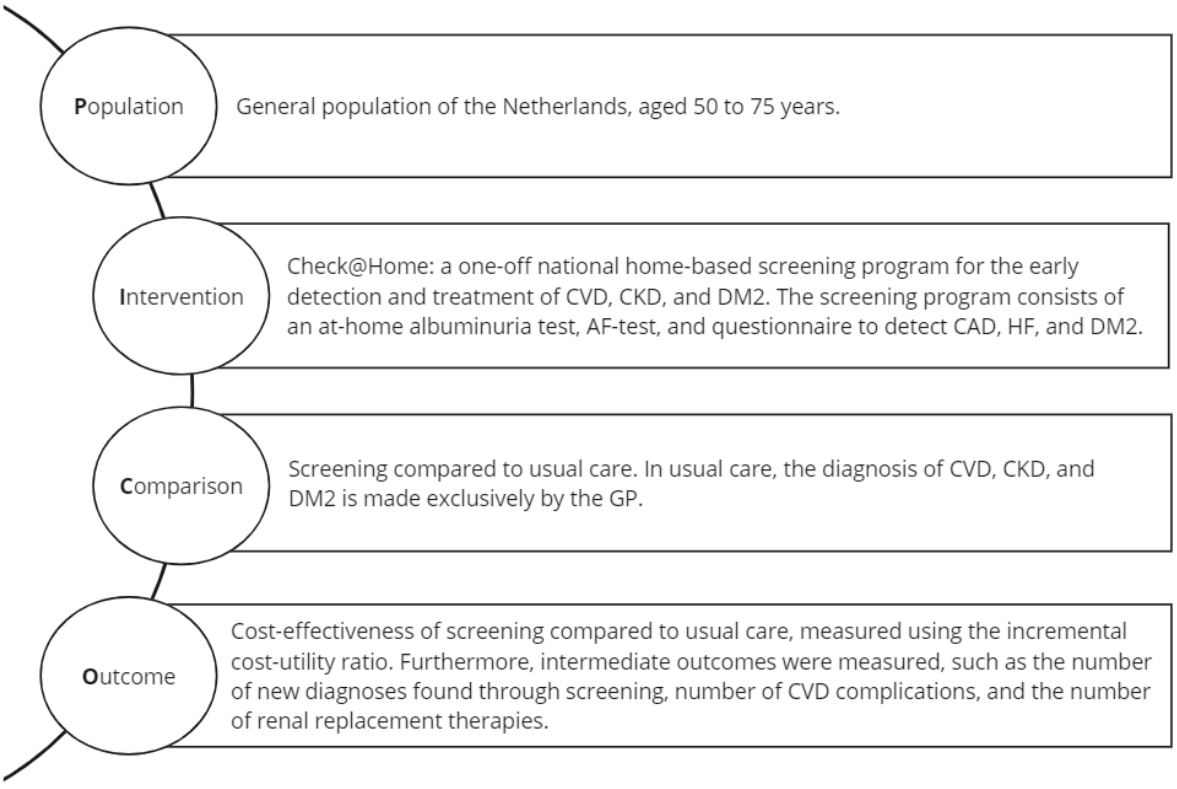



**Figure 1.** PICO framework

**Table 1.** Baseline characteristics of the population simulated in the model

| **Patient Characteristics** | **Value** | | **Source** |
|---|---|---|---|
| | *Men* | *Women* | |
| Gender (%) | 49.7 % | 50.3 % | (CBS, 2021) |
| Age in years (Mean / Range) | 61.7 (50-75) | 61.8 (50-75) | (CBS, 2021) |
| Smoker (%) | 17.2 % | 12.4 % | (VZinfo, 2023) |
| TC-level in mg/dL (Mean / Sd) | 5.6 (0.8) | 5.9 (0.9) | (Balder et al., 2017) |
| HDL-level in mg/dL (Mean / Sd) | 1.4 (0.3) | 1.7 (0.4) | (Balder et al., 2017) |
| Systolic blood pressure in mmHg (Mean / Sd) | 140 (18) | 133 (19) | (RIVM, 2012) |
| *Atrial Fibrillation* | | | |
| Diagnosed (%) | 3.5 % | 1.9 % | (Knoop et al., 2021) |
| Undiagnosed (%) | 0.8 % | 0.5 % | (Knoop et al., 2021) |
| *Coronary Artery Disease* | | | |
| Diagnosed (%) | 7.0 % | 2.8 % | (Nivel, 2022) |
| Undiagnosed (%) | 1.4 % | 0.6 % | (Nivel, 2022) |
| *Heart Failure* | | | |
| Diagnosed (%) | 1.2 % | 0.9 % | (VZinfo, 2022b) |
| Undiagnosed (%) | 1.4 % | 1.1 % | (VZinfo, 2022b) |
| *Chronic Kidney Disease* | | | |
| Diagnosed (%) | 4.4 % | 7.7 % | (Nierstichting, 2022a) |
| Undiagnosed (%) | 2.1 % | 3.7 % | (Nierstichting, 2022a) |
| *Prediabetes* | | | |
| Diagnosed (%) | 1.3 % | 1.0 % | (van Herpt et al., 2020) |
| Undiagnosed (%) | 11.9 % | 8.5 % | (van Herpt et al., 2020) |
| *Type 2 Diabetes* | | | |
| Diagnosed (%) | 9.0 % | 6.9 % | (VZinfo, 2022a) |
| Undiagnosed (%) | 1.6 % | 1.3 % | (VZinfo, 2022a) |
| *Overall Status* | | | |
| Diagnosed (%) | 26.5 % | 21.1 % | |
| Undiagnosed (%) | 19.2 % | 15.7 % | |
| Healthy (%) | 54.3 % | 63.2 % | |

The intervention evaluated in the health economic model was the Check@Home screening program. More specifically, we evaluated a one-off national home-based screening program consisting of an albuminuria test (i.e., urine collection device), an AF-test (i.e., Happitech), a questionnaire to detect CAD and HF (i.e., RED-CVD), and a questionnaire to detect DM2. In the screening strategy, the diagnosis of CVD, CKD, and DM2 could be made in two ways: (1) through the Check@Home screening program, or (2) at the GP. In the screening program, the target population received a one-time invitation to participate. Individuals who participated and tested true positive were diagnosed and treated earlier. We compared the screening intervention with usual care. In usual care, the diagnosis of CVD, CKD, and DM2 could exclusively take place at the GP.

We measured several outcomes to compare the health economic impact of the screening strategy with usual care. The primary outcomes were costs per patient, life years (LYs) per patient, and quality-adjusted life years (QALYs) per patient. The health effects and costs were compared

incrementally, resulting in the cost per QALY gained, also called the incremental cost-utility ratio (ICUR). We compared the ICUR against a willingness to pay (WTP) threshold of €20,000.

In addition to the primary outcomes, we measured secondary outcomes, including the number of new diagnoses found through screening, the number of CVD complications, the mean time until a CVD complication occurs, the number of individuals who progress to kidney failure, the number of kidney failure patients receiving renal replacement therapy (RRT) and palliative care, and the mean time until a CKD patient progresses to kidney failure. Furthermore, we examined the disease status of individuals at model initiation and the end of the time horizon.

The health economic evaluation was performed using a healthcare system perspective. Therefore, only the costs and effects of the Dutch healthcare system were considered. Societal costs and effects, such as productivity loss, patient- and family-related costs, and costs and effects in other sectors, were outside the scope of the current health economic analysis.

## 2.2. Model Structure

To assess the costs and health outcomes of the screening strategy and usual care strategy, we developed a non-constrained Discrete-Event Simulation (DES) model. The model and all analyses were performed using the statistical software R version 4.2.1 (R Core Team, n.d.). We used the package "Simmer", version 4.4.5, to develop the DES model. Simmer is a process-oriented and trajectory-based DES package for R (Ucar et al., 2019).

Choosing a DES model was based on expected future developments and envisioned possibilities for updating and extending the model. In the coming four to five years, the Check@Home study will gather individual patient data. A DES model has the capability to use such patient data to efficiently handle multiple competing events and select corresponding event times (Karnon et al., 2012). A DES model also enables the tracking of patient histories and incorporates patient characteristics that can change over time. Furthermore, the diagnostic and treatment pathways of CVD-, CKD-, and DM2-patients involve a series of related events. A DES model is well-suited to such situations (Karnon et al., 2012). Building a DES model now allows us to support model development in the future. Furthermore, it helps to understand what data is needed and where to focus in the future.

Figure 2 presents a high-level overview of the DES model structure. In the screening strategy, all individuals were invited to participate in the Check@Home screening program at the start of the simulation (i.e., grey box in Figure 2). In the usual care strategy, this was not the case.

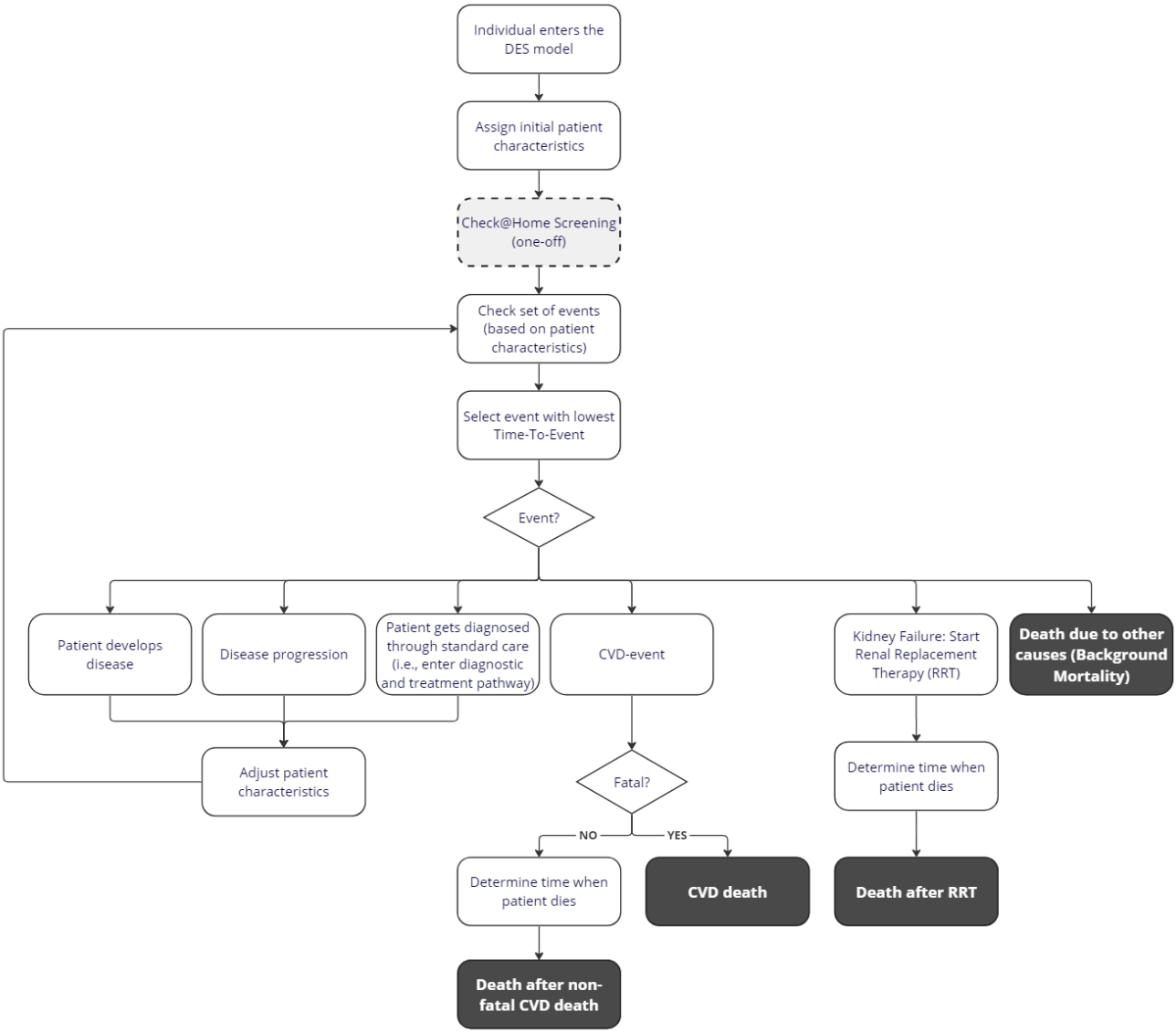



**Figure 2.** High-level overview DES model structure

In the health economic model, individuals were assigned a disease status (Table 2). The disease status indicated which disease an individual had, what disease stage they were in, and whether they were diagnosed or undiagnosed. If an individual had none of the five diseases, the individual was considered healthy. Based on the individual's disease status, the individual had a possible set of events (Appendix 5, Table 40). Subsequently, we applied the Event-Specific Distribution (ESD) approach to determine which event took place with the corresponding event time (Degeling et al., 2019). In this approach, a time $t_e$ to each competing event $e$ is drawn randomly from a time-to-event distribution $D_e$. Subsequently, the event that is first to occur (i.e., the event $e$ corresponding to the lowest drawn time-to-event $t_e$) is selected and will be simulated (Degeling et al., 2019). When individual patient data (IPD) is available, one can fit a time-to-event distribution based on the IPD. Since no IPD was accessible, we used evidence from the literature to derive time-to-event distributions.

**Table 2**. Defined disease status in the health economic model

| **Healthy** | **Chronic Kidney Disease** |
|---|---|
| 1. No Disease Present | 18. Diagnosed Mild CKD |
| **Atrial Fibrillation** | 19. Diagnosed Moderate CKD |
| 2. Diagnosed Paroxysmal AF | 20. Diagnosed Severe CKD |
| 3. Diagnosed Persistent AF | 21. Diagnosed Kidney Failure |
| 4. Diagnosed Permanent AF | 22. Undiagnosed mild CKD |
| 5. Undiagnosed Paroxysmal AF | 23. Undiagnosed moderate CKD |
| 6. Undiagnosed Persistent AF | 24. Undiagnosed severe CKD |
| 7. Undiagnosed Permanent AF | 25. Undiagnosed Kidney Failure |
| **Coronary Artery Disease** | **Type 2 Diabetes** |
| 8. Diagnosed CAD | 26. Diagnosed Prediabetes |
| 9. Undiagnosed CAD | 27. Diagnosed DM2 |
| **Heart Failure** | 28. Undiagnosed Prediabetes |
| 10. Diagnosed HF: NYHA-I | 29. Undiagnosed DM2 |
| 11. Diagnosed HF: NYHA-II | |
| 12. Diagnosed HF: NYHA-III | |
| 13. Diagnosed HF: NYHA-IV | |
| 14. Undiagnosed HF: NYHA-I | |
| 15. Undiagnosed HF: NYHA-II | |
| 16. Undiagnosed HF: NYHA-III | |
| 17. Undiagnosed HF: NYHA-IV | |

We considered five cardiovascular complications (CVD-events): ischemic stroke (IS), hemorrhage stroke (HS), myocardial infarction (MI), cardiac arrest (CA), and acute heart failure death (aHF). We assumed patients could only experience one CVD-event. In case the CVD-event was non-fatal, patients could recover or not recover from the event. We assumed that patients who do not recover experience permanent and lifelong disabilities, resulting in a reduction in quality of life. Patients who recover from a CVD-event, were assumed to return to their quality of life from before the event after three months. We considered seven possible ways to die in the model: (1) IS death, (2) HS death, (3) MI death, (4) CA death, (5) aHF death, (6) kidney failure death, and (7) death due to other causes (i.e., background mortality).

## 2.3. Structure Diagnostic and Treatment Pathway

This section presents the structure of the diagnostic and treatment pathway used in the DES model. Therefore, this section also answers the first sub-research question of this master thesis. The structure of the diagnostic and treatment pathway was based on NHG guidelines (NHG, 2017, 2018, 2019a, 2019b, 2021, 2022, 2023). Figure 3 presents a simplification of the pathway used in the DES model. A more detailed version can be found in Appendix 6. Table 5 provides an overview of the structural assumptions made regarding the diagnostic procedures and treatments provided. For an elaborate description of the five disease domains, including the symptoms, risk factors, complications, diagnostic options, and treatment options we refer to Appendix 1.

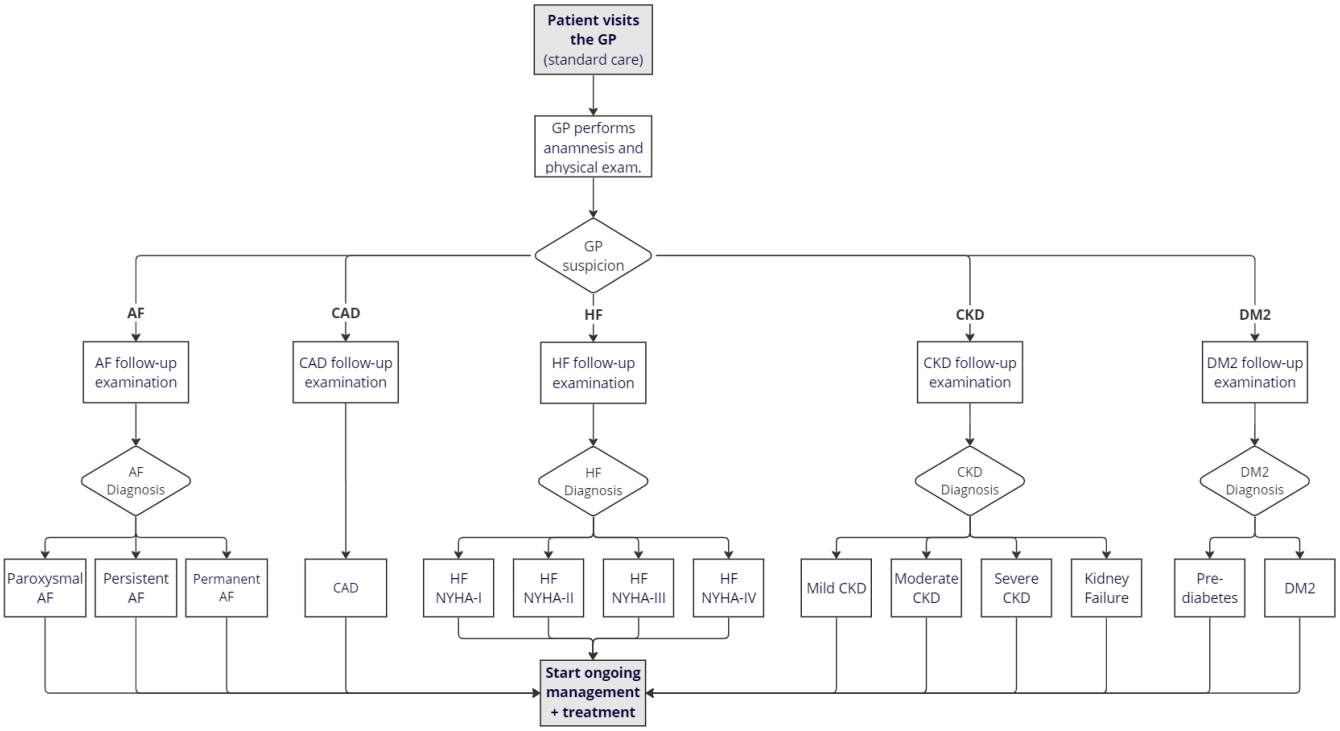



**Figure 3**. Simplification of the diagnostic and treatment pathway based on NHG guidelines

When a patient visits the GP, the GP starts with anamnesis (i.e., discuss medical history) and basic physical examinations (e.g., measuring blood pressure and listening to the heart frequency). After anamnesis and physical examination, we assumed that the disease suspicion of the GP is always correct (i.e., assumption: 100% sensitivity). Therefore, patients will always enter the right diagnostic and treatment trajectory.

### *Atrial Fibrillation*

In case AF is suspected, the GP starts with a standard ECG. A standard ECG detects persistent AF and permanent AF directly. Patients with paroxysmal AF get an additional Holter examination to observe the heart rhythm over a more extended period (i.e., 24-/48-hours). After the diagnosis, all patients enter a treatment and control plan corresponding to the diagnosed stage of the disease, consisting of medical therapy and control visits (see Table 5, assumption 4). Patients diagnosed with persistent AF are eligible for additional interventions in the form of cardioversion or ablation surgery. Ringborg et al. (2008) studied the cost and resource usage of AF treatments and interventions. Based on their analysis, we assumed that, of the persistent AF patients, 65.6% get cardioversion and 6.6% get an ablation surgery.

### *Coronary Artery Disease*

When CAD is suspected, the GP starts with a standard ECG. Subsequently, the GP conducts a laboratory test to measure the lipid profile. Next, the GP refers the patient to the cardiologist for additional examination. We assumed that the cardiologist conducts an additional laboratory test and echocardiogram. Furthermore, we assumed that the cardiologist performs a coronary angiography in 50% of the cases and a diagnostic scan (e.g., CT or MRI) in the remaining 50%. After the diagnosis, all CAD patients enter a treatment and control plan, consisting of medical therapy and control visits (see Table 5, assumption 6). Additionally, it was assumed that 5% of

CAD patients get a bypass surgery (i.e., rerouting blood flow) and 40% get an angioplasty (i.e., widening the narrowed artery).

*Heart Failure*

When HF is suspected, the GP starts with a standard ECG and laboratory test to measure the (NT-pro)BNP level. Subsequently, all HF patients are referred to the cardiologist. At the cardiologist, the patient gets an echocardiogram to measure the left ventricular ejection fraction (LVEF). The LVEF says something about the pump efficiency of the heart. Based on the reduction of LVEF, HF is generally classified into preserved ejection fraction (pEF, LVEF ≥ 50%), mid-range ejection fraction (mrEF, LVEF 40-49%), or reduced ejection fraction (rEF, LVEF < 40%). Based on the severity of the complaints, patients are assigned a NYHA-class. This is a functional classification based on the severity of the patients complaints. Table 3 describes the four functional NYHA-classes.

**Table 3.** Description of the four NYHA-classes (NHG, 2017)

| | |
|---|---|
| **NYHA Class I** | No limitation during exercise; normal physical activity does not cause excessive fatigue or shortness of breath |
| **NYHA Class II** | Some limitation during exercise; no complaints at rest, but normal physical exertion causes excessive fatigue or shortness of breath |
| **NYHA Class III** | Severe limitation during exercise; no or few complaints at rest, but light physical exertion causes excessive fatigue or shortness of breath |
| **NYHA Class IV** | No physical exertion possible without complaints; complaints at rest |

In this health economic analysis, it was decided to define the HF stages based on the NYHA classification. The reason for this is that pEF and rEF are two different types of HF. Where patients with pEF have HF due to a thick and stiff heart muscle, patients with rEF have HF because the heart muscle is thinner and weakened (Hartstichting, 2022). Therefore, it is uncommon to progress from pEF to mrEF to rEF. The NYHA classification is considered more functional than the LVEF classification. Moreover, the treatment a patient receives is often based on the patient's severity of complaints. After the diagnosis, patients enter a treatment and control plan corresponding to the diagnosed NYHA class (see Table 5, assumption 8 and 9) (NHG, 2021).

*Chronic Kidney Disease*

When CKD is suspected, the GP starts with a laboratory test to measure the patient's eGFR and ACR. Subsequently, CKD is classified into mild CKD, moderate CKD, severe CKD, or kidney failure (KDIGO, 2013) (Table 4).

**Table 4.** CKD stage distribution based on eGFR and ACR value (KDIGO, 2013)

| | | | **ACR (mg/mmol)** | | |
|---|---|---|---|---|---|
| | | | A1 | A2 | A3 |
| | | | < 3 | 3-30 | > 30 |
| **eGFR (ml/min/1.73m²)** | G1 | ≥ 90 | | Mild CKD | Moderate CKD |
| | G2 | 60-89 | | Mild CKD | Moderate CKD |
| | G3a | 45-59 | Mild CKD | Moderate CKD | Severe CKD |
| | G3b | 30-44 | Moderate CKD | Severe CKD | Severe CKD |
| | G4 | 15-29 | Severe CKD | Severe CKD | Severe CKD |
| | G5 | < 15 | Kidney failure | Kidney Failure | Kidney Failure |

If moderate or severe CKD is diagnosed, the patient is referred to a nephrologist for additional examination. We assumed that of the moderate and severe patients; everyone gets an additional

laboratory test. Furthermore, we assumed that one-third get an ultrasound, one-third get a CT scan, and one-third get an MRI scan. We also assumed that 50% of the cases get a kidney biopsy to examine the tissue of the kidney. After the diagnosis, patients enter a treatment and control plan corresponding to the diagnosed stage of the disease, consisting of medical therapy and control visits (see Table 5, assumption 11, 12, and 13).

It is considered extremely rare to be initially diagnosed with kidney failure. Therefore, in our health economic model we assumed it is not possible to be diagnosed with kidney failure. Instead we assumed that only diagnosed CKD patients can progress to kidney failure. Patients who progress to kidney failure (also called end-stage renal disease) are eligible for renal replacement therapies, such as kidney dialysis, kidney transplantation, and conservative treatment (i.e., palliative care). Section 2.6 describes the progression to kidney failure and renal replacement therapies in more detail.

*Type 2 Diabetes*

When DM2 is suspected, the GP performs a laboratory test to measure the patient's blood sugar level. With a blood sugar level between 6.1 mmol/L and 7.0 mmol/L, the patient is diagnosed with Impaired Glucose Tolerance, also called prediabetes. With a blood sugar level higher than 7.0 mmol/L, the patient is diagnosed with DM2. After the diagnosis, patients enter a treatment and control plan corresponding to the diagnosed stage of the disease (see Table 5, assumption 15) (NHG, 2023).

**Table 5.** Key assumptions diagnostic and treatment pathway.

| | |
|---|---|
| **1.** | The disease suspicion of the GP is always correct. Therefore, patients will always enter the right diagnostic trajectory and will not switch between the different trajectories. |
| **2.** | The diagnosis (disease and stage) of the GP is always correct, therefore, patients always enter the right treatment and control plan. |
| **3.** | All suspected AF cases get a standard ECG at the GP. Of the suspected paroxysmal AF patients, everyone gets a Holter examination. |
| **4.** | All patients diagnosed with AF (i.e., paroxysmal, persistent, and permanent AF) get the same treatment and control plan, consisting of: 2 controls at the GP per year to check progression and give lifestyle advice + medication to control the heart rhythm (calcium antagonists and digoxin). Patients diagnosed with permanent AF additionally get antithrombotic medication (NHG, 2017). Furthermore, 65.6% of the persistent AF patients get electric cardioversion and 6.6% get ablation surgery (Ringborg et al., 2008). |
| **5.** | All suspected CAD cases get a standard ECG at the GP. At the cardiologist, 100% get a laboratory test and echocardiogram. Moreover, 50% of the cases get a coronary angiography and the other 50% get a CT-, or MRI-scan. |
| **6.** | All patients diagnosed with CAD get the same treatment and control plan, consisting of: 1 control at the cardiologist per year and 2 controls at the GP per year. CAD patients also get medication to control the heart rhythm (calcium antagonists), cholesterol-lowering drug (statin), and antithrombotic medication (rivaroxaban). Furthermore, 5% of the CAD cases get a bypass surgery and 40% get a angioplasty. |
| **7.** | All suspected HF cases get a standard ECG and a laboratory test at the GP. Next, all HF cases are referred to the cardiologist, where everyone gets an echocardiogram. |
| **8.** | All patients diagnosed with heart failure NYHA-I/II/III get the same medical therapy, consisting of ACE-inhibitors and Diuretics. The amount of control visits is different. We assumed 1 visit to the GP per year for NYHA-I patients; 2 visits at the GP per year for NYHA-II patients; and 2 visits at the GP + 1 visit to the cardiologist per year for NYHA-III patients. |

| | |
|---|---|
| **9.** | All patients diagnosed with heart failure NYHA-IV get ACE-inhibitors and SGLT2-inhibitors. Additionally, it is assumed NYHA-IV patients visit the GP 2 times per year and the cardiologist 2 times per year. |
| **10.** | All suspected CKD patients get a laboratory test at the GP. If, based on the laboratory test, moderate or severe CKD is diagnosed, all these patients are referred to the nephrologist. It is assumed that 100% of the moderate and severe CKD cases get an additional laboratory test at the hospital. Moreover, 33% get and echo, 33% get a MRI, and 33% get a CT of the kidney / abdomen. Furthermore, it is assumed 50% gets a kidney biopsy. |
| **11.** | All patients diagnosed with mild CKD get the same treatment and control plan, consisting of: 1 control visit to the GP per year to check progression and give lifestyle advice + ACE-inhibitors. |
| **12.** | All patients diagnosed with moderate or severe CKD get the same medical therapy, consisting of ACE-inhibitors and SGLT2-inhibitors. Furthermore, it is assumed that patients diagnosed with moderate CKD visit the GP 2 times per year. Patients diagnosed with severe CKD visit the GP 1 time per and the nephrologist 3 times per year. |
| **13.** | All patients diagnosed with kidney failure (ESRD) get the same treatment and control plan, consisting of: 4 times per year control at the nephrologist + ACE-inhibitors and SGLT2-inhibitors. Besides, ESRD patients are eligible for renal replacement therapy. Patients above 85 years could not receive dialysis or kidney transplantation (conservative treatment). Patients above 75 years old could not undergo kidney transplantation, therefore received dialysis for the rest of their lives. Finally, 50% of the patients under 75 years old directly underwent kidney transplantation, the remaining underwent dialysis for three years before receiving a kidney transplantation. |
| **14.** | All patients with suspected DM2 get a laboratory test at the GP. It is assumed no other examinations are performed to diagnose DM2 or Prediabetes. |
| **15.** | All patients diagnosed with prediabetes get the same treatment and control plan, consisting of: 1 time per year control at the GP or to check progression and give lifestyle advice. All patients diagnosed with DM2 also get the same treatment and control plan, consisting of: 3 times per year control at the GP to give lifestyle advice. Moreover, they get ACE-inhibitors and SGLT2-inhibitors. |
| **16.** | Diagnosed patients all comply to the treatment plan provided. Furthermore, it is assumed that if patients under treatment progress to the next stage of disease, this will be discovered during one of the control visits. As a result, the treatment plan changes accordingly. |

## 2.4. Screening Strategy

The screening strategy evaluated in the health economic model is presented in Figure 4. We decided to implement a similar strategy as applied in the THOMAS study (van Mil et al., 2023). Therefore, patients with a positive home test received an invite for a follow-up test (FU1). When FU1 is positive, the patient is invited for extensive screening (ES) at a regional diagnostic center. If FU1 is negative, the patient is invited for a second follow-up test (FU2). When FU2 is positive, the patient is invited for ES since two of the three tests are positive. If FU2 is again negative, the patient is not invited for ES. Patients who decide to participate in ES get additional examinations to diagnose potential AF, CAD, HF, CKD, or DM2. Patients who test positive during ES are referred to their GP, where they enter the diagnostic and treatment trajectory described in section 2.3. We assumed that the screening process (i.e., three at-home tests and extensive screening at the diagnostic center) could detect all five disease domains.

The inputs used in the screening process are shown in Table 6. We assumed that the two follow-up tests were the same as the first at-home test received by participants. The at-home test consists of an albuminuria test, an AF-test (i.e., Happitech app), the RED-CVD questionnaire to detect CAD and HF, and a questionnaire to detect DM2 (Check@Home, 2022). For the participation probabilities, we used the probabilities described by van Mil et al. (2023). For the

cost of the home tests, we considered costs for sending the urine collection device for the albuminuria test (€3.82), sending back the device (€2.25), and the analysis of the result (€6.13). The last two costs were only charged if the individual participated. Furthermore, we assumed that the cost per individual for the Happitech app and the questionnaire was €1.00 each. The cost of extensive screening was set to €53.80, as in the THOMAS study (Pouwels et al., 2023).

Regarding the diagnostic performance of the at-home albuminuria test, we assumed a sensitivity of 96.6% and specificity of 97.3% to detect CKD (van Mil et al., 2023). For the AF-test, we considered a sensitivity of 98.1% and a specificity of 98.1% (Mol et al., 2020). The diagnostic performance of the RED-CVD questionnaire (i.e., to detect CAD and HF) and the questionnaire to detect DM2 has not yet been reported. Therefore, we assumed a sensitivity and specificity of 95%. For extensive screening, we assumed a 100% diagnostic performance. Therefore, only true positive patients were referred to the GP to enter the diagnostic and treatment pathway.

**Table 6.** Screening inputs: participation, costs, and diagnostic performance

| Description | Screening Input | Source |
|---|---|---|
| *Participation* | | |
| Probability to participate Check@Home test | 59.4 % | (van Mil et al., 2023) |
| Probability to participate follow-up test 1 | 92.8 % | (Pouwels et al., 2023) |
| Probability to participate follow-up test 2 | 92.8 % | (Pouwels et al., 2023) |
| Probability to participate extensive screening | 82.7 % | (Pouwels et al., 2023) |
| Probability to go to the GP after referral | 57.4 % | (Pouwels et al., 2023) |
| *Costs* | | |
| Sending the invite + UCD per individual | € 3.82 | (Pouwels et al., 2023) |
| Sending back the UCD + analysis per individual | € 8.38 | (Pouwels et al., 2023) |
| Extensive screening per individual | € 53.80 | (Pouwels et al., 2023) |
| Happitech and questionnaire per individual | € 2.00 | Assumption |
| *Diagnostic Performance* | | |
| Sensitivity CKD (home test) | 96.6 % | (van Mil et al., 2023) |
| Specificity CKD (home test) | 97.3 % | (van Mil et al., 2023) |
| Sensitivity AF (home test) | 98.1 % | (Mol et al., 2020) |
| Specificity AF (home test) | 98.1 % | (Mol et al., 2020) |
| Sensitivity CAD, HF, DM2 (home test) | 95.0 % | Assumption |
| Specificity CAD, HF, DM2 (home test) | 95.0 % | Assumption |
| Sensitivity extensive screening | 100.0 % | Assumption |
| Specificity extensive screening | 100.0 % | Assumption |

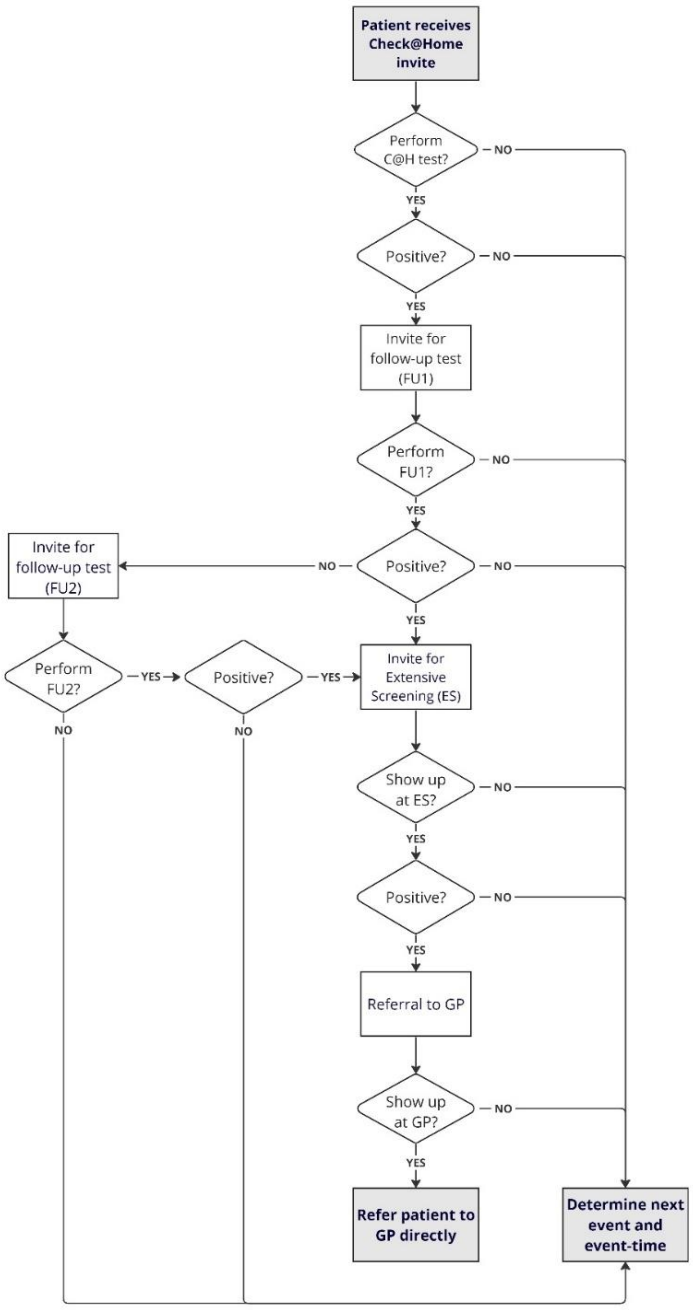



**Figure 4.** Design Screening Strategy

## 2.5. Disease Status at Model Initiation

At model initiation, all individuals are assigned initial characteristics. The characteristics, gender, age, smoking status, TC level, HDL level, and SBP are assigned as described in Appendix 7. We assumed that the gender and smoking status were fixed throughout the simulation time. All other patient characteristics were updated during the life course of individuals in the model. To determine the disease status at model initiation, we studied prevalence data per disease domain and, subsequently, calculated the probabilities of having the disease based on the individual's age and gender.

*Atrial Fibrillation Status*

We distinguished between seven different AF status: (1) diagnosed paroxysmal; (2) diagnosed persistent; (3) diagnosed permanent; (4) undiagnosed paroxysmal; (5) undiagnosed persistent; (6) undiagnosed permanent; (7) no AF. According to the Dutch Heart Association, the total number of existing diagnosed AF cases in the Netherlands was 362,700 (Knoop et al., 2021). Using population data from the Dutch National Statistics (CBS, 2021), this is equal to a prevalence of 2.1% in the Netherlands. The Dutch Heart Association also published evidence about the number of existing AF cases by age and gender in 2020 (Knoop et al., 2021). Together with general population data from the Dutch National Statistics (CBS, 2021), we calculated the prevalence rate by gender and age category. According to Chiang et al. (2012), the stage distribution of diagnosed paroxysmal, persistent, and permanent AF is 26.5%, 23.8%, and 49.6%. For this, they studied 9,816 AF patients from 831 sites in 26 countries. The Netherlands was not part of the study, but other European countries such as Belgium, Germany, and Sweden were included. Therefore, we assumed that the stage distribution from Chiang et al. (2012) is similar in the Netherlands. According to the Dutch Heart Association (Hartstichting, 2021), approximately 80,000 people in the Netherlands have AF but are undiagnosed (22.1% of diagnosed AF). We have no evidence about the stage distribution among the undiagnosed AF population. Therefore, at the start of the health economic model, we assumed that of the undiagnosed AF patients, 66.7% had paroxysmal AF, and 33.3% had persistent AF. This is a big structural assumption. Therefore, in Chapter 3, we evaluated the impact of this assumption on the results, by studying two other extreme scenarios. Table 7 presents the calculated probabilities for setting the AF status at model initiation in the base-case scenario (i.e., 33.3-66.7%).

**Table 7.** Probabilities initial AF status by age and gender

| | **Men** | | **Women** | |
|---|---|---|---|---|
| | **Aged 50-54** | **Aged 55-75** | **Aged 50-54** | **Aged 55-75** |
| Diagnosed Paroxysmal AF | 0.0021 | 0.0116 | 0.0009 | 0.0065 |
| Diagnosed Persistent AF | 0.0019 | 0.0104 | 0.0008 | 0.0058 |
| Diagnosed Permanent AF | 0.0039 | 0.0217 | 0.0016 | 0.0121 |
| Undiagnosed Paroxysmal AF | 0.0011 | 0.0064 | 0.0005 | 0.0036 |
| Undiagnosed Persistent AF | 0.0006 | 0.0032 | 0.0002 | 0.0018 |
| Undiagnosed Permanent AF | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| No AF | 0.9905 | 0.9465 | 0.9960 | 0.9702 |

*Coronary Artery Disease Status*

We distinguished between three different CAD status: (1) diagnosed CAD; (2) undiagnosed CAD; (3) no CAD. According to the Dutch Nivel Care Registry, there were an estimated 633,300 people diagnosed with coronary artery disease (i.e., angina pectoris and other ischemic heart diseases) in the Netherlands in 2021 (Nivel, 2022). The Nivel also published evidence about the prevalence rates by gender and age categories (Nivel, 2022). For this, we combined the prevalence rates of angina pectoris (ICPC: K74) and other ischemic heart diseases (ICPC: K76). Acute Myocardial Infarction (ICPC: K75) was excluded since myocardial infarctions were modelled as events in the health economic model (Section 2.3). The Check@Home consortium estimates that 21% of people with CAD are not aware of having the condition (Check@Home, 2022). Table 8 presents the calculated probabilities for setting the CAD status at individual initiation.

**Table 8.** Probabilities initial CAD status by age and gender

| | | Aged 50-54 | Aged 55-59 | Aged 60-64 | Aged 65-69 | Aged 70-75 |
|---|---|---|---|---|---|---|
| **Men** | Diagnosed CAD | 0.0230 | 0.0423 | 0.0705 | 0.1083 | 0.1521 |
| | Undiagnosed CAD | 0.0048 | 0.0089 | 0.0148 | 0.0227 | 0.0319 |
| | No CAD | 0.9722 | 0.9488 | 0.9147 | 0.8690 | 0.8160 |
| **Women** | Diagnosed CAD | 0.0117 | 0.0239 | 0.0374 | 0.0588 | 0.0785 |
| | Undiagnosed CAD | 0.0025 | 0.0050 | 0.0079 | 0.0123 | 0.0165 |
| | No CAD | 0.9858 | 0.9711 | 0.9547 | 0.9289 | 0.9050 |

*Heart Failure Status*

We distinguished between nine different HF status: (1) diagnosed HF – NYHA-I; (2) diagnosed HF – NYHA-II; (3) diagnosed HF – NYHA-III; (4) diagnosed HF – NYHA-IV; (5) undiagnosed HF – NYHA-I; (6) undiagnosed HF – NYHA-II; (7) undiagnosed HF – NYHA-III; (8) undiagnosed HF – NYHA-IV; (9) no HF. The total number of diagnosed HF cases was approximately 241,300 in the Netherlands in 2021 (VZinfo, 2022b). The Dutch Ministry of Health, Welfare, and Sports also published evidence about the prevalence of HF by age and gender in 2021. Norhammar et al. (2023) studied the stage distribution of HF patients per NYHA class. In their study, 629,440 patients with HF were identified across 11 countries: 13.4% had NYHA class I, 37.7% had NYHA class II, 36.2% had NYHA class III, and 12.7% had NYHA class IV. Moreover, the Check@Home consortium estimated that 255,000 people in the Netherlands have HF but are undiagnosed (Check@Home, 2022). We have no evidence about the stage distribution among the undiagnosed HF population. Therefore, at the start of the health economic model, we assumed that of the undiagnosed HF patients, 66.7% had NYHA-I and 33.3% had NYHA-II. Again, this is a major structural assumption. Therefore, in Chapter 3, we evaluated the impact of this assumption on the results, by studying two extreme scenarios. Table 9 presents the calculated probabilities for setting the HF status at individual initiation in the base-case scenario.

**Table 9.** Probabilities initial HF status by age and gender

| | | Aged 50-54 | Aged 55-59 | Aged 60-64 | Aged 65-69 | Aged 70-75 |
|---|---|---|---|---|---|---|
| **Men** | Diagnosed NYHA-I | 0.0005 | 0.0010 | 0.0018 | 0.0030 | 0.0053 |
| | Diagnosed NYHA-II | 0.0015 | 0.0028 | 0.0051 | 0.0085 | 0.0150 |
| | Diagnosed NYHA-III | 0.0014 | 0.0026 | 0.0049 | 0.0081 | 0.0144 |
| | Diagnosed NYHA IV | 0.0005 | 0.0009 | 0.0017 | 0.0029 | 0.0051 |
| | Undiagnosed NYHA-I | 0.0028 | 0.0051 | 0.0094 | 0.0159 | 0.0280 |
| | Undiagnosed NYHA-II | 0.0014 | 0.0026 | 0.0047 | 0.0079 | 0.0140 |
| | Undiagnosed NYHA-III | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | Undiagnosed NYHA IV | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | No HF | 0.9918 | 0.9850 | 0.9724 | 0.9537 | 0.9181 |
| **Women** | Diagnosed NYHA-I | 0.0005 | 0.0007 | 0.0012 | 0.0021 | 0.0036 |
| | Diagnosed NYHA-II | 0.0014 | 0.0019 | 0.0035 | 0.0058 | 0.0100 |
| | Diagnosed NYHA-III | 0.0014 | 0.0018 | 0.0034 | 0.0056 | 0.0096 |
| | Diagnosed NYHA IV | 0.0005 | 0.0006 | 0.0012 | 0.0020 | 0.0034 |
| | Undiagnosed NYHA-I | 0.0027 | 0.0035 | 0.0066 | 0.0109 | 0.0187 |
| | Undiagnosed NYHA-II | 0.0013 | 0.0018 | 0.0033 | 0.0055 | 0.0093 |
| | Undiagnosed NYHA-III | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | Undiagnosed NYHA IV | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | No HF | 0.9922 | 0.9897 | 0.9809 | 0.9681 | 0.9455 |

*Chronic Kidney Disease Status*

We distinguished between nine different CKD status: (1) diagnosed mild CKD; (2) diagnosed moderate CKD; (3) diagnosed severe CKD; (4) diagnosed kidney failure; (5) undiagnosed mild CKD; (6) undiagnosed moderate CKD; (7) undiagnosed severe CKD; (8) undiagnosed kidney

failure; (9) no CKD. According to data from the Dutch Kidney Foundation, approximately 1.7 million people in the Netherlands have diagnosed CKD (Nierstichting, 2022a). Van Blijderveen et al. (2014) performed a population-based cohort study on the prevalence and incidence of CKD in the Netherlands. They published the prevalence rates of CKD for men and women in different age categories. Furthermore, the Nivel Care Registry published evidence about the stage distribution among diagnosed CKD patients in general care. The stage distribution for mild CKD, moderate CKD, severe CKD, and kidney failure was 58.3%, 24.2%, 17.1%, and 0.38%, respectively (Leemrijse et al., 2021). In addition to diagnosed CKD patients, the Dutch Kidney Foundation estimates that 800,000 people in the Netherlands have CKD but are undiagnosed (47.1% of diagnosed CKD) (Nierstichting, 2022a). We have no evidence about the stage distribution among the undiagnosed HF population. Therefore, at the start of the health economic model, we assumed that of the undiagnosed CKD patients, 66.7% had mild CKD, and 33.3% had moderate CKD. In Chapter 3, we evaluated the impact of this assumption on the results by studying two extreme scenarios. Table 10 presents the calculated probabilities for setting the CKD status at individual initiation in the base-case scenario.

**Table 10.** Probabilities initial CKD status by age and gender

| | | **Aged 50-54** | **Aged 55-59** | **Aged 60-64** | **Aged 65-69** | **Aged 70-75** |
|---|---|---|---|---|---|---|
| **Men** | Diagnosed mild | 0.0067 | 0.0141 | 0.0288 | 0.0563 | 0.1018 |
| | Diagnosed moderate | 0.0022 | 0.0046 | 0.0093 | 0.0182 | 0.0330 |
| | Diagnosed severe | 0.0010 | 0.0022 | 0.0045 | 0.0087 | 0.0158 |
| | Diagnosed ESRD | 0.0001 | 0.0002 | 0.0004 | 0.0008 | 0.0014 |
| | Undiagnosed mild | 0.0031 | 0.0066 | 0.0135 | 0.0264 | 0.0477 |
| | Undiagnosed moderate | 0.0016 | 0.0033 | 0.0067 | 0.0132 | 0.0238 |
| | Undiagnosed severe | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | Undiagnosed ESRD | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | No CKD | 0.9853 | 0.9691 | 0.9367 | 0.8764 | 0.7764 |
| **Women** | Diagnosed mild | 0.0147 | 0.0261 | 0.0489 | 0.0838 | 0.1420 |
| | Diagnosed moderate | 0.0048 | 0.0085 | 0.0158 | 0.0271 | 0.0460 |
| | Diagnosed severe | 0.0023 | 0.0041 | 0.0076 | 0.0130 | 0.0220 |
| | Diagnosed ESRD | 0.0002 | 0.0004 | 0.0007 | 0.0011 | 0.0019 |
| | Undiagnosed mild | 0.0069 | 0.0122 | 0.0229 | 0.0392 | 0.0665 |
| | Undiagnosed moderate | 0.0035 | 0.0061 | 0.0115 | 0.0196 | 0.0333 |
| | Undiagnosed severe | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | Undiagnosed ESRD | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| | No CKD | 0.9676 | 0.9426 | 0.8926 | 0.8161 | 0.6881 |

### *Estimated Glomerular Filtration Rate and Albumin-Creatine Ratio*

After setting the CKD status of an individual, the individual was assigned an estimated Glomerular Filtration Rate (eGFR) and Albumin-Creatine Ratio (ACR). Based on the data from the NHANES study, a US population-based study (1999 – 2006, N = 18,026), KDIGO (2013) determined the percentage of the US population by eGFR and ACR category. We assumed that the Dutch population aged 50-75 years followed the same distribution as the US population. Table 11 was used to determine the eGFR and ACR. Within the eGFR and ACR range, a uniform distribution was used to set the values accordingly. We assumed that the range in eGFR G1 is 90-100 and the range in eGFR G5 is 1-14. Furthermore, the range in ACR A1 is 0.01-2.99, and the range in ACR A3 is 30.01-60.00. For example, a mild CKD patient (yellow) has a 24.7% probability to have an eGFR higher than or equal to 90 ml/min/1.73m2 and an ACR between 3 an 30 mg/mmol (calculation: $1.9/\ 7.7 \cdot 100\% = 24.7\%$).

**Table 11.** Proportion (%) of US adult population by eGFR and ACR. Green: No CKD, Yellow: mild CKD, Orange: Moderate CKD, Red: Severe CKD, Dark Red: Kidney Failure

| | | | ACR (mg/mmol) | | | |
|---|---|---|---|---|---|---|
| | | | A1 | A2 | A3 | |
| | | | < 3 | 3-30 | > 30 | |
| **eGFR (ml/min/1.73m²)** | G1 | ≥ 90 | 55.6 % | 1.9 % | 0.4 % | 57.9 % |
| | G2 | 60-89 | 32.9 % | 2.2 % | 0.3 % | 35.4 % |
| | G3a | 45-59 | 3.6 % | 0.8 % | 0.2 % | 4.6 % |
| | G3b | 30-44 | 1.0 % | 0.4 % | 0.2 % | 1.6 % |
| | G4 | 15-29 | 0.2 % | 0.1 % | 0.1 % | 0.4 % |
| | G5 | < 15 | 0.0 % | 0.0 % | 0.1 % | 0.1 % |
| | | | 93.2 % | 5.4 % | 1.3 % | 100 % |

*Diabetes Type 2 Status*

We distinguished five DM2-status: (1) diagnosed prediabetes; (2) diagnosed DM2; (3) undiagnosed prediabetes; (4) undiagnosed DM2; (5) no prediabetes/DM2. According to the Dutch Diabetes Foundation, approximately 1.1 million people have prediabetes, and 1.2 million people have diabetes in the Netherlands. Of those 1.2 million people with diabetes, it is estimated that 90.4% have DM2 (Diabetes Fonds, n.d.-b). The Dutch Ministry of Health, Welfare, and Sports (VZinfo, 2022a) published data about the prevalence of diabetes among men and women in different age categories, used to calculate the probabilities of having diagnosed DM2. In addition to diagnosed DM2 patients, the Check@Home consortium estimates that approximately 200,000 people in the Netherlands have undiagnosed DM2 (Check@Home, 2022). Compared to the total number of existing DM2 cases in the Netherlands, this is a ratio of 19.1%.

As part of the Rotterdam Study, van Herpt et al. (2020) studied the prevalence of prediabetes (i.e., pre-stage of DM2) for men and women in different age categories. These prevalence rates were used to determine whether a new individual has prediabetes or not. In the base-case scenario of our DES model, we assumed that 90% of the prediabetes patients are undiagnosed. Table 12 presents the calculated probabilities for setting the DM2 status at individual initiation.

**Table 12.** Probabilities initial DM2 status by age and gender

| | | Aged 50-54 | Aged 55-59 | Aged 60-64 | Aged 65-69 | Aged 70-74 |
|---|---|---|---|---|---|---|
| **Men** | Diagnosed prediabetes | 0.0100 | 0.0200 | 0.0200 | 0.0190 | 0.0190 |
| | Diagnosed DM2 | 0.0647 | 0.0915 | 0.1224 | 0.1624 | 0.1963 |
| | Undiagnosed prediabetes | 0.0900 | 0.1800 | 0.1800 | 0.1710 | 0.1710 |
| | Undiagnosed DM2 | 0.0124 | 0.0175 | 0.0234 | 0.0311 | 0.0375 |
| | No DM2 | 0.8229 | 0.6910 | 0.6542 | 0.6165 | 0.5762 |
| **Women** | Diagnosed prediabetes | 0.0060 | 0.0130 | 0.0130 | 0.0150 | 0.0150 |
| | Diagnosed DM2 | 0.0478 | 0.0660 | 0.0899 | 0.1197 | 0.1502 |
| | Undiagnosed prediabetes | 0.0485 | 0.1051 | 0.1051 | 0.1213 | 0.1213 |
| | Undiagnosed DM2 | 0.0540 | 0.1170 | 0.1170 | 0.1350 | 0.1350 |
| | No DM2 | 0.8831 | 0.7914 | 0.7629 | 0.7074 | 0.6711 |

## 2.6. Events

We distinguished 22 events: (1) AF development; (2) CAD development; (3) HF development; (4) CKD development; (5) DM2 development; (6) Progression: paroxysmal to persistent AF; (7) Progression: persistent to permanent AF; (8) Progression: NYHA-I to NYHA-II; (9) Progression: NYHA-II to NYHA-III; (10) Progression: NYHA-III to NYHA-IV; (11) Progression: mild to moderate CKD; (12) Progression: moderate to severe CKD; (13) Progression: severe CKD to ESRD; (14) Progression: prediabetes to DM2; (15) Transient Ischemic Attack; (16) Ischemic Stroke; (17)

Hemorrhage Stroke; (18) Myocardial Infarction; (19) Cardiac Arrest; (20) Acute HF-death; (21) Death due to other cause; and (22) Diagnosis through standard care. In the remainder of this section, we describe how we modeled the events and the structural assumptions made.

*Disease Development*

In reality, individuals who already have a disease can also develop a new disease. However, we have no data available on the risk of comorbidity, the chance of disease progression, and the increased risk of CVD-events for all disease combinations. Therefore, in the DES model, we assumed that only healthy individuals can develop a new disease. For those healthy individuals who develop a disease, it is assumed they develop the first stage of the disease. Therefore, individuals who develop AF get paroxysmal AF; individuals who develop HF develop NYHA-I; individuals who develop CKD develop mild CKD; and individuals who develop diabetes first develop prediabetes. Healthy individuals who develop a disease are considered undiagnosed until they get diagnosed through standard care or Check@Home screening. To determine when a patient develops a disease, we used reported cumulative risks at different time intervals. Next, we applied linear interpolation to determine the event time for developing the disease.

Although we did not consider comorbidity, we made an exception for prediabetes patients. If we assumed that prediabetes patients could only progress to DM2 and not develop another disease, the CVD risk would be lower in prediabetes patients compared to healthy individuals. The reason for this is that healthy individuals are at risk of developing all five diseases, while prediabetes patients could only progress to DM2. Therefore, healthy individuals could develop diseases with higher CVD risk than DM2. To prevent this, we assumed that prediabetes patients can progress to DM2 and are at risk of developing AF, CAD, HF, or CKD. When a prediabetes patient developed a new disease, we assumed that the new disease was the dominant disease, and prediabetes was no longer considered. Furthermore, we distinguished between diagnosed and undiagnosed prediabetes patients. Diagnosed prediabetes patients had a similar risk of disease development to healthy individuals. In contrast, undiagnosed prediabetes patients were assumed to have an increased 10% cumulative risk.

To determine when an individual develops a disease, we studied the period and lifetime risks from literature. As part of the Rotterdam Study, a population-based cohort study in the Netherlands, Heeringa et al. (2006) studied the cumulative risk and lifetime risk of AF at different ages in men and women (n=6432) (Table 13). To determine when someone develops AF, we used the cumulative risks closest to the individual's age. Therefore, age only had an effect per 5-year interval. Subsequently, we used linear interpolation to set the event time. The reported lifetime risks were assumed to be the cumulative risk at age 105. We assumed that individuals could not get older than 105 years, as they have already died from other causes.

**Table 13.** Cumulative risk of AF in different time periods at different ages stratified by gender

| Age (years) | Period risk (%) of developing AF in 5-years intervals | | | | | | Lifetime risk (95% CI) |
|---|---|---|---|---|---|---|---|
| | 5 years | 10 years | 15 years | 20 years | 25 years | 30 years | |
| **Men** | | | | | | | |
| 55 | 0.8 | 2.8 | 5.4 | 9.6 | 15.2 | 20.1 | 23.8 (15.6-26.9) |
| 60 | 2.1 | 4.7 | 8.9 | 14.6 | 19.6 | | 23.3 (15.1-26.4) |
| 65 | 2.8 | 7.3 | 13.4 | 18.7 | | | 22.7 (14.3-25.8) |
| 70 | 5.0 | 11.6 | 17.5 | | | | 21.9 (13.3-25.2) |
| 75 | 7.9 | 14.9 | | | | | 20.2 (11.1-23.8) |
| 80 | 9.2 | | | | | | 16.1 (6.4-20.3) |
| 85 | | | | | | | 11.8 (1.3-17.2) |
| **Women** | | | | | | | |
| 55 | 0.0 | 1.0 | 2.9 | 7.2 | 11.1 | 16.3 | 22.2 (14.7-24.8) |
| 60 | 0.9 | 2.9 | 7.2 | 11.2 | 16.4 | | 22.3 (14.8-24.9) |
| 65 | 2.0 | 6.4 | 10.6 | 19.1 | | | 22.1 (14.6-24.8) |
| 70 | 4.6 | 9.0 | 14.7 | | | | 21.1 (13.4-23.8) |
| 75 | 4.8 | 11.2 | | | | | 18.3 (10.2-21.2) |
| 80 | 7.4 | | | | | | 15.3 (7.4-18.9) |
| 85 | | | | | | | 11.8 (1.9-14.1) |

To determine when someone develops HF, we used a similar approach as for AF. As part of the Rotterdam Study, Bleumink et al. (2004) studied the cumulative and lifetime risk of HF at different ages in men and women in the Netherlands (n=7983) (Table 14). We assumed that the reported lifetime risk was equal to the cumulative risk at age 105. Again, linear interpolation was used to set the event time for developing HF.

**Table 14.** Cumulative risk of HF in different time periods at different ages stratified by gender

| Age (years) | Period risk (%) of developing HF in 5-years intervals | | | | | | | Lifetime risk |
|---|---|---|---|---|---|---|---|---|
| | 5 years | 10 years | 15 years | 20 years | 25 years | 30 years | 35 years | |
| **Men** | | | | | | | | |
| 55 | 0 | 2.8 | 6.8 | 13.4 | 19.6 | 27.9 | 31.6 | 33.0 |
| 65 | 4.2 | 11.4 | 18.2 | 27.1 | 31.2 | | | 32.7 |
| 75 | 9.5 | 22.0 | 27.7 | | | | | 29.8 |
| 85 | 16.2 | | | | | | | 22.4 |
| **Women** | | | | | | | | |
| 55 | 1.0 | 1.8 | 3.0 | 6.2 | 11.2 | 17.5 | 24.3 | 28.5 |
| 65 | 1.2 | 4.6 | 10.0 | 16.7 | 24.0 | | | 28.5 |
| 75 | 6.2 | 14.1 | 22.6 | | | | | 27.9 |
| 85 | 14.3 | | | | | | | 23.3 |

For AF and HF, the period and lifetime risk were obtained from the Rotterdam study. We assumed that these risks also include the risk of developing undiagnosed AF and HF. For CAD, no population-based cohort studies were found reporting the 5-year risks and lifetime risk of developing CAD. Therefore, we approximated these risks using incidence data from the Dutch Nivel Care Registry. The Nivel published evidence about the incidence rates of diagnosed angina pectoris (ICPC: K74) and diagnosed other chronic ischemic heart disease (ICPC: K76) by gender and age category in 2021 (maximum age category: > 85 years) (Nivel, 2022). The incidence rates of the Nivel only include the incidence of diagnosed patients. Therefore, we increased the incidence rates by 21%, as this is the estimated proportion of people unaware of having CAD (Check@Home, 2022). Subsequently, we converted the incidence rates into probabilities, as presented in Table 15. Next, linear interpolation was used to set the event time for developing CAD.

**Table 15.** Risk of developing CAD in different time periods by gender and age

| Age (years) | Risk of developing CAD (%) in different 5-years time intervals by gender for different ages | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 yrs | 10 yrs | 15 yrs | 20 yrs | 25 yrs | 30 yrs | 35 yrs | 40 yrs | 45 yrs | 50 yrs | 55 yrs |
| **Men** | | | | | | | | | | | |
| 50 | 1.6 | 3.9 | 7.0 | 10.5 | 14.5 | 18.4 | 22.0 | 26.7 | 31.2 | 35.3 | 39.2 |
| 55 | 2.3 | 5.5 | 9.1 | 13.1 | 17.2 | 20.8 | 25.6 | 30.1 | 34.3 | 38.3 | |
| 60 | 3.3 | 6.9 | 11.0 | 15.2 | 18.9 | 23.8 | 28.4 | 32.7 | 36.8 | | |
| 65 | 3.8 | 8.0 | 12.3 | 16.1 | 21.2 | 26.0 | 30.4 | 34.6 | | | |
| 70 | 4.4 | 8.8 | 12.8 | 18.1 | 23.0 | 27.7 | 32.1 | | | | |
| 75 | 4.7 | 8.8 | 14.3 | 19.5 | 24.4 | 29.0 | | | | | |
| 80 | 4.4 | 10.2 | 15.6 | 20.7 | 25.5 | | | | | | |
| 85+ | 6.0 | 11.7 | 17.1 | 22.1 | | | | | | | |
| **Women** | | | | | | | | | | | |
| 50 | 0.8 | 2.2 | 4.1 | 6.7 | 9.4 | 12.5 | 15.7 | 18.6 | 21.4 | 24.0 | 26.6 |
| 55 | 1.4 | 3.3 | 5.9 | 8.7 | 11.8 | 15.1 | 17.9 | 20.7 | 23.4 | 26.0 | |
| 60 | 2.0 | 4.6 | 7.5 | 10.5 | 13.9 | 16.8 | 19.6 | 22.3 | 25.0 | | |
| 65 | 2.7 | 5.6 | 8.7 | 12.1 | 15.1 | 18.0 | 20.8 | 23.5 | | | |
| 70 | 3.0 | 6.2 | 9.7 | 12.8 | 15.7 | 18.6 | 21.4 | | | | |
| 75 | 3.3 | 6.9 | 10.1 | 13.1 | 16.1 | 18.9 | | | | | |
| 80 | 3.7 | 7.0 | 10.2 | 13.2 | 16.1 | | | | | | |
| 85+ | 3.4 | 6.7 | 9.8 | 12.9 | | | | | | | |

Inker et al. (2015) studied the cumulative risk of developing CKD (CKD stage 3 or higher) in the general population of Iceland for men and women of different ages (Table 16). To determine when someone develops CKD in our DES model, a similar approach was used for developing AF and HF. Therefore, linear interpolation was used to set the event time for developing CKD. No lifetime risks were provided by Inker et al. (2015). We assumed that the lifetime risk (i.e., the risk at age 105) is 5% higher than the last reported cumulative risk.

**Table 16.** Cumulative risk of CKD in different time periods at different ages stratified by gender

| Age (years) | Risk of developing CKD (%) in different time intervals by gender and age (95% CI) | | | |
|---|---|---|---|---|
| | 5 years | 10 years | 20 years | 30 years |
| **Men** | | | | |
| 55 | 1.2 (0.7-1.7) | 3.2 (2.3-4.1) | 11.1 (9.4-12.8) | 20.7 (18.1-23.3) |
| 65 | 2.7 (1.8-3.6) | 9.0 (7.3-10.7) | 19.8 (17.0-22.6) | |
| 75 | 8.2 (6.0-10.3) | 13.9 (10.9-17.0) | | |
| 80 | 7.4 (4.5-10.4) | 10.4 (6.5- 14.2) | | |
| **Women** | | | | |
| 55 | 2.0 (1.3-2.7) | 6.0 (4.9-7.1) | 18.9 (17.0-20.9) | 34.9 (31.7-38.0) |
| 65 | 5.3 (4.2-6.5) | 14.1 (12.3-16.0) | 31.6 (28.3-34.9) | |
| 75 | 10.0 (7.8-12.2) | 22.2 (18.4-26.0) | | |
| 80 | 15.0 (11.0-19.0) | 24.9 (19.1-30.7) | | |

Ligthart et al. (2016) studied the 10-year and lifetime risks of developing prediabetes in the Netherlands (Table 17). We assumed that the lifetime risk from Ligthart et al. (2016) is at age 105. Linear interpolation was used to set the event time for developing prediabetes.

**Table 17.** 10-year risk and lifetime risk of Prediabetes by age

| Age (years) | 10-year risk (%) + 95% CI | Lifetime risk (%) + 95% CI |
|---|---|---|
| 55 | 13.2 (11.4-15.0) | 44.5 (42.5-46.6) |
| 65 | 19.3 (17.7-20.9) | 37.6 (35.6-39.5) |
| 75 | 19.1 (17.3-20.9) | 25.8 (23.7-28.0) |
| 85 | 11.9 (9.5-14.4) | 13.1 (10.4-15.7) |

*Progression*

The five disease domains concern progressive diseases. Treatment, such as medical therapy and lifestyle advice, can help to delay progression. To model progression, we obtained progression probabilities and the relative effectiveness of treatment on progression from the literature (Table 20). The exponential distribution was used to set an event time for disease progression. In our model, we assumed progression was unidirectional. Therefore, patients could not regress to a less severe stage of disease.

Holmqvist et al. (2015) studied the progression of paroxysmal AF to persistent and permanent AF. In a study population of 6,235 patients, 1,479 patients showed AF progression during an 18-month follow-up (i.e., annual probability: 16.5%) (Holmqvist et al., 2015). For the deterministic analysis, this results in an annual progression rate of 0.1803. This progression rate was used for the progression from paroxysmal to persistent AF and from persistent to permanent AF. According to Gunawardene and Willems (2022), most clinical studies show that medical therapy does not affect the progression of AF. Therefore, we assumed that AF progression is equal in patients under medical therapy (RR: 1.00).

Packer et al. (2015) studied the progression of patients with HF under the treatment of Sacubitril/Valsartan. Sacubitril/Valsartan is an ACE-inhibitor, a drug diagnosed HF patients receive (Table 5, assumption 11). In a study population of 4,187 patients, 225 patients showed a worsening NYHA classification after 12 months (i.e., annual probability: 5.4%). Therefore, for the deterministic analysis an annual progression rate of 0.0552 was used. This progression rate was used for progression to one NYHA class higher. We did not find progression rates for patients who are not under the treatment of ACE-inhibitors. According to Wei et al. (2020), the relative risk reduction of ACE-inhibitors versus Placebo on overall cardiovascular events is 0.71 (95% CI: 0.60-0.83). We assumed that the relative risk reduction of ACE-inhibitors on progression is equal to the risk reduction on overall cardiovascular events. For the deterministic analysis, this results in an annual progression rate of 0.0778 in patients who are not on medication of ACE-inhibitors (i.e., annual progression probability: 7.5%).

According to Elbasha et al. (2017), the annual progression probability from mild CKD to moderate CKD is 9.6%, from moderate CKD to severe CKD is 13.7%, and from severe CKD to kidney failure is 8.1%. We assumed that only diagnosed patients can progress from severe CKD to kidney failure. In the diagnostic and treatment pathway, we assumed that all patients diagnosed with CKD receive ACE-inhibitors. Furthermore, we assumed that patients with moderate CKD, severe CKD, and kidney failure additionally receive SGLT2-ihibitors (Table 5). According to Heerspink et al. (2020), the progression from any CKD stage to kidney failure is reduced by 36% in patients with SGLT2-inhibitors (dapagliflozin) versus placebo (RR: 0.64, 95% CI: 0.50-0.82, N = 2,152). For mild CKD patients on medication of ACE-inhibitors, we assumed the same progression reduction as reported in HF patients on medication of ACE-inhibitors: 0.71 (95% CI: 0.60-0.83) (Wei et al., 2020).

CKD patients who progress to kidney failure are eligible for renal replacement therapy. We assumed that patients with kidney failure above 85 years cannot receive dialysis or kidney transplantation (Table 5, assumption 13). These patients get conservative treatment. Conservative treatment is generally more focused on maintaining health-related quality of life than potentially increasing survival (Voorend et al., 2022). When patients end up in conservative treatment, we the time until the patient dies is uniformly distributed from 6 to 31 months (Voorend et al., 2022). Patients above 75 years old could not undergo kidney transplantation and,

therefore, receive dialysis for the rest of their lives. 50% of the patients under 75 years old directly underwent kidney transplantation; the remaining underwent dialysis for three years before receiving a kidney transplantation. The Dutch Kidney Foundation (2022b) published evidence about the expected remaining lifetime after starting with dialysis or receiving a kidney transplantation by different age categories (Table 18). We assumed that the expected remaining lifetime of these patients was fixed.

**Table 18**. Expected remaining lifetime in years for dialysis and transplantation patients

| | **Expected remaining lifetime (years)** | |
|---|---|---|
| **Age Category** | **Dialysis** | **Transplantation** |
| 50-54 years | 8 | 18 |
| 55-59 years | 7 | 15 |
| 60-64 years | 6 | 12 |
| 65-69 years | 5 | 10 |
| 70-74 years | 4 | 7 |
| 75+ years | 3 | 5 |

Finally, for the progression from prediabetes to DM2, we used input from van Herpt et al. (2020). They studied the 10-year and lifetime risk of progressing from prediabetes to DM2 by age category (Table 19). To determine when someone progresses from prediabetes to DM2, we used the cumulative risks closest to the individual's age. We assumed that the lifetime risk is the risk at age 105. Next, linear interpolation was used to set the event time for progressing from prediabetes to DM2.

**Table 19.** 10-year risk and lifetime risk (95% CI) of progressing from prediabetes to DM2, WHO criteria (van Herpt et al., 2020)

| **Age (years)** | **10-year risk (%)** | **Lifetime risk (%)** |
|---|---|---|
| 55 | 34.2 (22.9 to 45.5) | 74.2 (68.5 to 79.9) |
| 65 | 35.5 (29.4 to 41.5) | 61.9 (56.4 to 67.3) |
| 75 | 39.3 (32.7 to 46.0) | 49.1 (42.3 to 55.8) |
| 85 | 21.1 (13.1 to 29.1) | 21.1 (13.1 to 29.1) |

In the diagnostic and treatment pathway, we assumed that all diagnosed prediabetes patients get lifestyle advice (Table 5, assumption 15). According to Gossain and Aldasouqi (2010), the progression from prediabetes to DM2 is reduced by 49% (RR: 0.51, 95% CI: 0.44–0.60) in patients adherent to lifestyle advice compared with standard advice.

**Table 20.** Annual progression probabilities (deterministic analysis) and relative effectiveness of treatment.

| **Progression** | | |
|---|---|---|
| *Description* | *Annual progression probability (deterministic analysis)* | *Source* |
| Paroxysmal to Persistent AF | 0.165 | (Holmqvist et al., 2015) |
| Persistent to Permanent AF | 0.165 | (Holmqvist et al., 2015) |
| HF NYHA-I to NYHA-II | 0.075 | (Wei et al., 2020; Zueger et al., 2018) |
| HF NYHA-II to NYHA-III | 0.075 | (Wei et al., 2020; Zueger et al., 2018) |
| HF NYHA-III to NYHA-IV | 0.075 | (Wei et al., 2020; Zueger et al., 2018) |
| Mild to Moderate CKD | 0.096 | (Elbasha et al., 2017) |
| Moderate to Severe CKD | 0.137 | (Elbasha et al., 2017) |
| Severe CKD to Kidney Failure | 0.081 | (Elbasha et al., 2017) |
| **Relative Effectiveness** | | |
| *Description* | *RR (95% CI)* | *Source* |
| AF Treatment | 1.00 | Assumption (AF treatment has no effect on progression) |
| HF Treatment (i.e., ACE-inhibitors) | 0.71 (0.60-0.83) | (Wei et al., 2020) |
| CKD Treatment (i.e., ACE-inhibitors for mild CKD) | 0.71 (0.60-0.83) | (Wei et al., 2020) |
| CKD Treatment (i.e., SGLT2-inhibitors for moderate CKD, severe CKD, and Kidney Failure) | 0.64 (0.50-0.82) | (Heerspink et al., 2020) |
| DM2 Treatment (i.e., lifestyle advice) | 0.51 (0.44-0.60) | (Gossain & Aldasouqi, 2010) |

### *Cardiovascular Events*

To determine the event time of a CVD-event, we used a 5-step approach (figure 5). First, we examine the characteristics of an individual. Depending on the characteristics, we used different CVD risk prediction models to calculate the 10-year CVD risk. For healthy individuals aged younger than 70 years, we applied the SCORE2 prediction model (S. Hageman et al., 2021). For patients older than or equal to 70 years, SCORE2-OP was used. (T. I. de Vries et al., 2021). Inputs for SCORE2 and SCORE2-OP are age, gender, smoking status, systolic blood pressure, TC level, HDL level, and risk region (the Netherlands is considered a low-risk region). To calculate the 10-year risk of DM2 patients, we applied the SCORE2-Diabetes model (Pennells et al., 2023). For patients with CKD, we used the SCORE2 model with CKD add-on risk (based on the eGFR and ACR) (Matsushita et al., 2023).

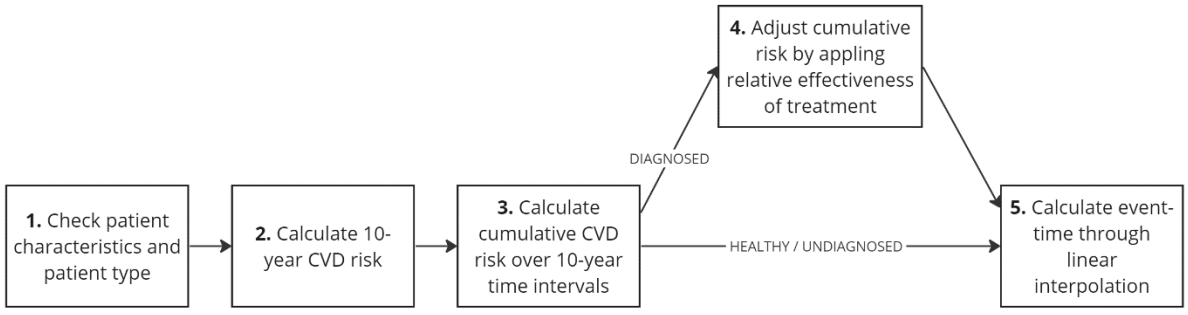



**Figure 5.** Five-step approach for determining the event time of a CVD-event

To calculate the 10-year risk of patients with CAD and patients who had a TIA in the past, we applied the SMART2 model (S. H. J. Hageman et al., 2022). The SMART2 model includes previously identified cardiovascular diseases, such as acute coronary syndrome, angina pectoris, coronary revascularization, and TIA (S. H. J. Hageman et al., 2022). Extra inputs in the SMART2 model are the eGFR, the use of aspirin or other equivalent antithrombotic drugs, year(s) since diagnosis, and

the hsCRP value. For the last two, population means were used as defined by Hageman et al. (2022): respectively 1 year since diagnosis, and a CRP of 2.4 mg/L.

AF, HF, and prediabetes are not included in the SMART2 model. To calculate the 10-year CVD risk of patients with AF, HF, or prediabetes, we obtained hazard ratios (HR) from literature for the increased risk of overall CVD-events (Table 21). The HRs were applied on the result of SCORE2 (or SCORE2-OP for individuals aged ≥ 70 years). According to Odutayo et al. (2016), AF is associated with an 96% increased risk of major cardiovascular events (HR: 1.96, 95%CI: 1.53-2.51). Research from the European Society of Cardiology showed that permanent AF doubled the risk of CVD-events compared to paroxysmal AF (ESC, 2014). Therefore, in the DES model, we decided to double the overall CVD risk for permanent AF patients (i.e., HR: 2.92 in deterministic analysis, 192% increased risk). In patients with prediabetes, the increased risk of overall CVD-events is 13% (Mando et al., 2021). For patients with HF, a similar approach was used. However, the HRs depended on the NYHA class the patient was in. In patients with NYHA-I, it was assumed that their 10-year CVD risk was equal to the SCORE2 outcome. Ahmed et al. (2006) published evidence about the increased risk of all-cause mortality in patients with NYHA-II to NYHA-IV compared to patients with NYHA-I. We assumed that the increased risk in overall CVD-events is equal to the increased risk in all-cause mortality as defined by Ahmed et al. (2006). Therefore, the following HRs were used to determine the increased CVD risk in patients with HF: 1.54, 2.56, and 8.46, respectively, for NYHA-II, NYHA-III, and NYHA-IV.

**Table 21.** Hazard ratios for CVD risk in AF, HF, and Prediabetes patients

| Disease Domain | Mean (HR) | 95% CI | Source |
|---|---|---|---|
| AF: Paroxysmal | 1.96 | 1.53 – 2.51 | (Odutayo et al., 2016) |
| AF: Persistent | 1.96 | 1.53 – 2.51 | (Odutayo et al., 2016) |
| AF: Permanent | 2.92 | - | Assumption |
| HF: NYHA-I | 1.00 | - | Assumption |
| HF: NYHA-II | 1.54 | 1.02 – 2.32 | (Ahmed et al., 2006) |
| HF: NYHA-III | 2.56 | 1.64 – 4.01 | (Ahmed et al., 2006) |
| HF: NYHA-IV | 8.46 | 3.57 – 20.03 | (Ahmed et al., 2006) |
| Prediabetes | 1.13 | 1.09 – 1.18 | (Mando et al. 2021) |

After calculating the 10-year CVD risk we also calculated the 10-year CVD risk, 10-, 20-, 30-, 40-, and 50-years from now, by holding all individual characteristics constant except age (i.e., increase age in steps of 10 years). Subsequently, we calculated the cumulative risk over 10-year time intervals. We assumed that the period risk was constant within every 10-year time interval. For those individuals without a treatment plan (i.e., healthy and undiagnosed individuals), we applied linear interpolation to derive the event time of a CVD-event.

For patients diagnosed with a disease, we assumed that everyone complied with the treatment plan provided by the GP and medical specialist (Table 5, assumption 16). To determine how much the cumulative CVD risk of an individual is reduced due to treatment, we applied the relative effectiveness of medical therapy to the cumulative risk. Table 22 provides an overview of the relative effectiveness collected from the literature, of different medical therapies versus placebo on overall CVD-events. If patients received a combination of medical therapies, the medical therapy with the lowest hazard ratio (i.e., the largest risk reduction) was used in the DES model. Patients diagnosed with prediabetes do not receive medical therapy. Instead, they receive lifestyle advice. We assumed that patients diagnosed with prediabetes who receive lifestyle

advice have a cumulative CVD risk equal to the SCORE2 outcome (i.e., equal to healthy individuals).

**Table 22.** Relative effectiveness of treatment / medical therapies on overall cardiovascular risk

| Medication / Drug | Mean (RR) | 95% CI | Source |
|---|---|---|---|
| Calcium antagonist | 0.79 | 0.63-0.98 | (Turnbull et al., 2005) |
| Antithrombotic (DOAC, Rivaroxaban) | 0.74 | 0.65-0.86 | (Connolly et al., 2018) |
| Cholesterol-lowering drug (Statin) | 0.75 | 0.70-0.81 | (Taylor et al., 2013) |
| ACE-inhibitors | 0.71 | 0.60-0.83 | (Wei et al., 2020) |
| SGLT2-inhibitors | 0.79 | 0.62-0.87 | (Tsai et al., 2022) |

In the DES model, we distinguish between five possible CVD-events: IS, HS, MI, CA, and aHF (incorporated in the inclusion criteria of SCORE2 and SMART2). To determine which of the five CVD-events occur we studied their contribution to mortality and hospitalizations. Table 23 shows the absolute number of deaths and hospitalizations (i.e., clinical admission, day admission, and observation) in the Netherlands in 2020 (CBS, 2023b, 2023c). We have assumed that there was no overlap between the total number of deaths and hospitalizations. The proportions between the types of CVD-events were used to decide which event takes place. The proportions were assumed to be fixed for every individual in the model.

**Table 23.** Absolute number of death and hospitalizations of IS (ICD-10: I63-I64), HS (ICD-10: I61-I62), MI (ICD-10: I21), CA (ICD-10: I46), and aHF (ICD-10: I50) in 2020 in the Netherlands

| | IS | HS | MI | CA | aHF |
|---|---|---|---|---|---|
| **Death** | 5,126 | 1,720 | 4,718 | 1,719 | 7,139 |
| **Hospitalization** | 30,800 | 6,350 | 35,080 | 3,265 | - |
| **Total** | 35,936 | 8,070 | 39,798 | 4,984 | 7,139 |
| *Proportion* | *37.46 %* | *8.41 %* | *41.49 %* | *5.2 %* | *7.44 %* |

When a CVD-event occurred, we needed to know whether the event was fatal or non-fatal. The Dutch Heart Association published data about the 30-day mortality probabilities of IS, HS, and MI by gender and age category in 2020 (Hartstichting, 2021). In the DES model, we used these 30-day mortality probabilities to determine whether the event was fatal. For CA, evidence from Zijlstra et al. (2016) was used, who published the probabilities of fatal and non-fatal CA by age category in six different regions in the Netherlands.

When the CVD-event was non-fatal, patients could either recover or not recover from the event. According to the Stroke Foundation (2020), it is estimated that 50% of the patients who survive a stroke (IS or HS) will live with permanent or lifelong disabilities (i.e., lower quality of life). We assumed that the remaining 50% completely recovers (i.e., no impact on quality of life). Of the patients experiencing an MI, we assumed that all patients recover from it and have no risk for permanent disabilities. According to Zijlstra et al. (2016), 90% of the patients who survive a CA recover after the event. We assumed that the remaining 10% did not recover from the CA and had permanent and lifelong disabilities. Table 24 shows the probabilities of a fatal and non-fatal event, as well as the probabilities to recover and not recover from the event.

**Table 24.** Probability fatal vs. non-fatal and probability recovered vs. not recovered.

| **Fatal vs. Non-Fatal** | | | |
|---|---|---|---|
| | *Fatal* | *Non-Fatal* | *Source* |
| **Ischemic Stroke** | | | |
| Aged 50-54 | 0.045 | 0.955 | (Hartstichting, 2021) |
| Aged 55-74 | 0.065 | 0.935 | (Hartstichting, 2021) |
| Aged 75-84 | 0.126 | 0.874 | (Hartstichting, 2021) |
| Aged ≥ 85 | 0.260 | 0.740 | (Hartstichting, 2021) |
| **Hemorrhage Stroke** | | | |
| Aged 50-54 | 0.234 | 0.766 | (Hartstichting, 2021) |
| Aged 55-74 | 0.278 | 0.722 | (Hartstichting, 2021) |
| Aged 75-84 | 0.402 | 0.598 | (Hartstichting, 2021) |
| Aged ≥ 85 | 0.536 | 0.464 | (Hartstichting, 2021) |
| **Myocardial Infarction** | | | |
| Aged 50-54 | 0.033 | 0.967 | (Hartstichting, 2021) |
| Aged 55-74 | 0.065 | 0.935 | (Hartstichting, 2021) |
| Aged 75-84 | 0.172 | 0.828 | (Hartstichting, 2021) |
| Aged ≥ 85 | 0.307 | 0.693 | (Hartstichting, 2021) |
| **Cardiac Arrest** | | | |
| Aged < 70 years | 0.700 | 0.300 | (Zijlstra et al., 2016) |
| Aged 70-79 years | 0.815 | 0.185 | (Zijlstra et al., 2016) |
| Aged ≥ 80 | 0.912 | 0.088 | (Zijlstra et al., 2016) |
| **Recover vs. Not Recovered** | | | |
| *CVD-Event* | *Recover* | *Not Recovered* | *Source* |
| Ischemic Stroke | 0.50 | 0.50 | (The Stroke Foundation, 2020) |
| Hemorrhage Stroke | 0.50 | 0.50 | (The Stroke Foundation, 2020) |
| Myocardial Infarction | 1.00 | 0.00 | Assumption |
| Cardiac Arrest | 0.90 | 0.10 | (Zijlstra et al., 2016) |

Finally, to determine when patients who survived a CVD-event die, we examined the 5-year mortality probability after an IS, HS, MI, and CA (Amacher et al., 2022; Hartstichting, 2021). We converted the 5-year mortality probabilities into rates and assumed that the risk of dying was constant over five years (Table 25). Subsequently, we used the exponential distribution to set the event time. Furthermore, we assumed that patients who did not die in five years died later from other causes.

**Table 25.** 5-year mortality for IS, HS, MI, and CA

| | **5-year mortality probability** | **Rate (deterministic analysis)** | **Source** |
|---|---|---|---|
| **Ischemic Stroke** | | | |
| Aged 50-54 | 0.105 | 0.022 | (Hartstichting, 2021) |
| Aged 55-74 | 0.262 | 0.061 | (Hartstichting, 2021) |
| Aged 75-84 | 0.543 | 0.157 | (Hartstichting, 2021) |
| Aged 85+ | 0.807 | 0.329 | (Hartstichting, 2021) |
| **Hemorrhage Stroke** | | | |
| Aged 50-54 | 0.335 | 0.082 | (Hartstichting, 2021) |
| Aged 55-74 | 0.466 | 0.125 | (Hartstichting, 2021) |
| Aged 75-84 | 0.725 | 0.258 | (Hartstichting, 2021) |
| Aged 85+ | 0.883 | 0.429 | (Hartstichting, 2021) |
| **Myocardial Infarction** | | | |
| Aged 50-54 | 0.077 | 0.016 | (Hartstichting, 2021) |
| Aged 55-74 | 0.184 | 0.041 | (Hartstichting, 2021) |
| Aged 75-84 | 0.498 | 0.138 | (Hartstichting, 2021) |
| Aged 85+ | 0.776 | 0.299 | (Hartstichting, 2021) |
| **Cardiac Arrest** | | | |
| All ages | 0.770 | 0.294 | (Amacher et al., 2022) |

*Transient Ischemic Attack*

A Transient Ischemic Attack (TIA) is a temporary blockage of a blood vessel in the brain due to a blood clot. Complete recovery usually occurs within half an hour (Hartstichting, n.d.). The ICD-10 code of a TIA is not included in the SCORE2 and SMART2 risk prediction models. To approximate the cumulative risk of experiencing a TIA, we used the incidence rates by gender and age category reported by the Dutch Nivel Care Registry (Nivel, 2022). The incidence rates of the Nivel only include those of diagnosed TIA patients. Undiagnosed TIA was excluded from the model, as this event was deemed to have a neglectable impact on cost and health effects. With the incidence rates from Nivel, we calculated the expected number of occurrences for different time intervals by gender and age. Subsequently, we converted the occurrences (i.e., rates) into probabilities, as presented in Table 26. Next, linear interpolation was used to set the event time for experiencing a TIA. Individuals in the same gender-age category were assumed to have the same risk of experiencing a TIA.

**Table 26.** Calculated cumulative probabilities (%) of experiencing a TIA in different time intervals for different ages.

| Age (years) | Risk of experiencing a TIA (%) in different 5-years time intervals by gender for different ages | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 5 yrs | 10 yrs | 15 yrs | 20 yrs | 25 yrs | 30 yrs | 35 yrs | 40 yrs | 45 yrs | 50 yrs | 55 yrs |
| **Men** | | | | | | | | | | | |
| 50 | 0.5 | 1.1 | 2.2 | 3.6 | 5.4 | 8.4 | 12.0 | 16.1 | 20.1 | 23.8 | 27.4 |
| 55 | 0.7 | 1.7 | 3.1 | 5.0 | 8.0 | 11.6 | 15.7 | 19.7 | 23.4 | 27.0 | |
| 60 | 1.1 | 2.5 | 4.3 | 7.4 | 11.0 | 15.2 | 19.1 | 22.9 | 26.6 | | |
| 65 | 1.4 | 3.3 | 6.4 | 10.0 | 14.2 | 18.3 | 22.1 | 25.8 | | | |
| 70 | 1.9 | 5.0 | 8.7 | 13.0 | 17.1 | 21.0 | 24.7 | | | | |
| 75 | 3.1 | 6.9 | 11.3 | 15.5 | 19.4 | 23.2 | | | | | |
| 80 | 3.9 | 8.4 | 12.7 | 16.8 | 20.7 | | | | | | |
| 85+ | 4.7 | 9.2 | 13.4 | 17.5 | | | | | | | |
| **Women** | | | | | | | | | | | |
| 50 | 0.4 | 1.0 | 1.9 | 3.1 | 4.9 | 7.2 | 10.2 | 14.4 | 18.4 | 22.2 | 25.8 |
| 55 | 0.6 | 1.5 | 2.7 | 4.5 | 6.9 | 9.9 | 14.1 | 18.1 | 21.9 | 25.5 | |
| 60 | 0.9 | 2.1 | 3.9 | 6.3 | 9.3 | 13.5 | 17.6 | 21.4 | 25.1 | | |
| 65 | 1.2 | 3.1 | 5.5 | 8.5 | 12.8 | 16.8 | 20.7 | 24.4 | | | |
| 70 | 1.9 | 4.3 | 7.4 | 11.7 | 15.8 | 19.7 | 23.4 | | | | |
| 75 | 2.5 | 5.6 | 10.0 | 14.2 | 18.2 | 22.0 | | | | | |
| 80 | 3.2 | 7.7 | 12.0 | 16.1 | 20.0 | | | | | | |
| 85+ | 4.7 | 9.1 | 13.3 | 17.4 | | | | | | | |

*Background Mortality*

Table 27 presents the annual background mortality probabilities by age and gender in the Netherlands in 2021. The probabilities were derived from the Dutch National Statistics (CBS, 2023c). The ICD-10 codes included in the SCORE2, SCORE2-OP, SCORE2-Diabetes, SMART2 model, and the ICD-10 codes dedicated to CKD (N17-N19) were removed from the causes of death. From an age of 105, we assumed a 100% probability of dying from other causes. To determine the event time of these deaths, we used the probabilities from Table 27 and calculated the cumulative risks. Subsequently, we used linear interpolation to set the event time for death due to other causes.

**Table 27.** Annual background mortality probabilities by gender and age categories.

| Age Category | Men | Women |
|---|---|---|
| 50-54 | 0.0026 | 0.0021 |
| 55-59 | 0.0045 | 0.0035 |
| 60-64 | 0.0071 | 0.0058 |
| 65-69 | 0.0121 | 0.0091 |
| 70-74 | 0.0196 | 0.0134 |
| 75-79 | 0.0355 | 0.0237 |
| 80-84 | 0.0605 | 0.0407 |
| 85-89 | 0.1109 | 0.0851 |
| 90-94 | 0.1911 | 0.1645 |
| 95-99 | 0.3097 | 0.2687 |
| 100-104 | 0.5420 | 0.4688 |
| 105 | 1.0000 | 1.0000 |

*Diagnosis through Standard Care*

To determine when an undiagnosed patient visits the GP, we categorized the different disease stages into low, middle, high, and very high stages. Subsequently, we assumed that patients with a "low" stage have a 10% probability of visiting the GP. Of the patients in the "middle" stages, we assumed a 50% probability of visiting the GP. Patients with a "high" stage were assumed to have an 85% probability of visiting the GP. Patients in "very high" stages were assumed to have a 100% probability of visiting the GP. This is a major structural assumption in the health economic model. Therefore, in Chapter 3, we will evaluate the impact of this assumption on the results, by studying two extreme scenarios. In a future health economic model, it is crucial to verify this assumption with clinical experts or retain data from empirical studies.

Furthermore, if patients visit the GP, we assumed that the visit takes place within five years (uniformly distributed). Undiagnosed patients who progressed to kidney failure were assumed to be diagnosed right away and immediately start RRT.

**Table 28.** Low, middle, high, and very high stage categorization.

| | |
|---|---|
| **Low Stages: 10%** | HF: NYHA-I |
| | CKD: Mild |
| | Prediabetes |
| **Middle Stages: 50%** | AF: Paroxysmal |
| | AF: Persistent |
| | HF: NHYA-II |
| | CKD: Moderate |
| **High Stages: 85%** | AF: Permanent |
| | CAD |
| | HF: NYHA-III |
| | Type 2 Diabetes |
| **Very High Stages: 100%** | HF: NYHA-IV |
| | CKD: Severe |
| | Kidney Failure |

## 2.7. Utilities

Quality of life was measured using utility values. Guidelines from the National Healthcare Institute of the Netherlands recommend EQ-5D utility to measure quality of life in health economic evaluations (ZiN, 2016). The utility values associated with every health condition are provided in Table 29. We assumed the utility values were the same for diagnosed and undiagnosed patients. Patients with prediabetes are assumed to have the same quality of life as

healthy individuals since prediabetes is commonly an asymptomatic condition (Bansal, 2015). When an individual transits to a health condition with a higher utility value, we assumed that the individual retained the utility value from before the transition. Therefore, no higher utility values were accepted over time. This is, for example, the case when a healthy 65-year-old develops HF NYHA-I (from a utility of 0.839 to 0.855). An exception was made for patients who receive kidney transplantation after dialysis because the quality of life significantly improves after transplantation.

For patients who experienced an IS or HS, we distinguished between the quality of life in the first three months after the event and subsequent months. When the utility before the event was lower than the utility of the CVD-event itself, we assumed that the utility remained the same. This is, for example, the case when an HF NYHA-IV patient experiences a stroke. For patients experiencing an MI or CA, we applied a utility decrement (van Hulst et al., 2022).

**Table 29.** Utility Values (Mean, Standard deviation, Number of observations)

| Health Status | Mean | Sd / 95% CI | N | Source |
|---|---|---|---|---|
| Healthy individuals aged 50-59 | 0.857 | SD: 0.183 | 186 | (Versteegh et al., 2016) |
| Healthy individuals aged 60-69 | 0.839 | SD: 0.179 | 158 | (Versteegh et al., 2016) |
| Healthy individuals aged 70+ | 0.852 | SD: 0.148 | 106 | (Versteegh et al., 2016) |
| Paroxysmal AF | 0.790 | SD: 0.230 | 493 | (Doyle et al., 2011) |
| Persistent AF | 0.800 | SD: 0.210 | 233 | (Doyle et al., 2011) |
| Permanent AF | 0.730 | SD: 0.260 | 380 | (Doyle et al., 2011) |
| CAD | 0.671 | SE: 0.046 | - | (Petersohn et al., 2020) |
| HF – NYHA-I | 0.855 | 95% CI: 0.845-0.864 | - | (Göhler et al., 2009) |
| HF – NYHA-II | 0.771 | 95% CI: 0.761-0.781 | - | (Göhler et al., 2009) |
| HF – NYHA-III | 0.673 | 95% CI: 0.665-0.690 | - | (Göhler et al., 2009) |
| HF – NYHA-IV | 0.532 | 95% CI: 0.480-0.584 | - | (Göhler et al., 2009) |
| Mild CKD | 0.800 | 95% CI: 0.690-1.000 | 45 | (Cooper et al., 2020) |
| Moderate CKD | 0.800 | 95% CI: 0.680-1.000 | 173 | (Cooper et al., 2020) |
| Severe CKD | 0.740 | 95% CI: 0.620-0.850 | 423 | (Cooper et al., 2020) |
| Kidney Failure (ESRD) | 0.570 | SD: 0.330 | 22 | (Lee et al., 2005) |
| Dialysis | 0.440 | SD: 0.320 | 60 | (Lee et al., 2005) |
| Post Kidney Transplantation | 0.710 | SD: 0.270 | 125 | (Lee et al., 2005) |
| DM2 | 0.815 | 95% CI: 0.808-0.823 | - | (Redenz et al., 2023) |
| Stroke (IS/HS): Recovered (month: 0-3) | 0.655 | 95% CI: 0.527-0.698 | - | (van Hulst et al., 2022) |
| Stroke (IS/HS): Recovered (month : 3+) | 0.752 | 95% CI: 0.605-0.809 | - | (van Hulst et al., 2022) |
| Stroke (IS/HS): Not Recovered (month: 0-3) | 0.167 | 95% CI: 0.134-0.170 | - | (van Hulst et al., 2022) |
| Stroke (IS/HS): Not Recovered (month: 3+) | 0.449 | 95% CI: 0.361-0.469 | - | (van Hulst et al., 2022) |
| Decrement for MI | -0.0557 | 95% CI: -0.0337;-0.0777 | - | (van Hulst et al., 2022) |
| Decrement for CA | -0.0557 | 95% CI: -0.0337;-0.0777 | - | Assumption |
| Death | 0.000 | | | Assumption |

## 2.8. Costs

Table 30 provides an overview of the costs used in the diagnostic and treatment pathway, as well as the costs used for RRT and CVD-events. If costs were expressed in another currency than Euros, the average exchange rate from the corresponding year was used. Furthermore, all costs were indexed to costs in 2022, using the CPI from Dutch National Statistics (CBS, 2023a).

For the costs related to CVD-events we used the health economic evaluation from van Hulst et al. (2022) as a reference. They looked at the acute and post-event costs made for AF patients experiencing an IS, HS, and MI. The acute costs are those made in the first three months after the event (e.g., ambulance, hospitalization, Etc.). The post-event costs are those made after the event. The post-event costs were expressed in 3-month cycles. Van Hulst et al. (2022) explained that patients stay in the post-event state until the next CVD-event occurs. In our DES model, we

converted the post-event costs into annual costs. Van Hulst et al. (2022) also distinguish between minor (Rankin Scale 1-2) and major events (Rankin Scale 3-5). In our DES model, we assumed that minor events indicate that a patient recovered from the event, while major events indicate that a patient did not recover. Furthermore, we assumed that the costs incurred after a CA are similar to those incurred after an MI.

**Table 30.** Overview costs used in diagnostic and treatment pathway, for renal replacement therapy, and for CVD-events (indexed to EURO 2022)

| **DIAGNOSTIC COSTS** | | |
|---|---|---|
| **Description** | **Cost** | **Source** |
| Visit at GP | € 41 | (Hakkaart-van Roijen et al., 2015) |
| Visit at cardiologist / nephrologist | € 112 | (Hakkaart-van Roijen et al., 2015) |
| Standard ECG | € 52 | (NZa, 2023) |
| Laboratory test (blood / urine test) | € 88 | (Koenraadt, 2019) |
| Holter examination + assessment | € 209 | (MST, 2023; Ringborg et al., 2008) |
| Echocardiogram | € 107 | (Hakkaart-van Roijen et al., 2015) |
| Exercise ECG | € 176 | (Ringborg et al., 2008) |
| Coronary angiography | € 1,280 | (ZiN, 2017) |
| Scan to diagnose CAD (either a CT- or MRI-scan) | € 1,333 | (MST, 2023) declaration code: 15A631 |
| Kidney biopsy (to diagnose CKD, assumption 50% of the cases get a biopsy in the diagnostic pathway) | € 364 | (MST, 2023) declaration code: 050519 / 080077 |
| Scan of the kidney (average cost of an echo, CT, or MRI of the abdomen) | € 248 | (MST, 2023) declaration code: 087070 / 087097 / 087042 |
| **TREATMENT COSTS (ANNUALLY)** | | |
| **Description** | **Cost** | **Source** |
| Paroxysmal AF treatment and control | € 299 | |
| *Control: 2x visit to the GP per year* | *€ 82* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: calcium antagonists* | *€ 103* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: digoxin* | *€ 114* | (Farmacotherapeutisch Kompas, n.d.) |
| Persistent AF treatment and control | € 299 | |
| *Control: 2x visit to the GP per year* | *€ 82* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: calcium antagonists* | *€ 103* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: digoxin* | *€ 114* | (Farmacotherapeutisch Kompas, n.d.) |
| Permanent AF treatment and control | € 1,691 | |
| *Control: 2x visit to the GP per year* | *€ 82* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: calcium antagonists* | *€ 103* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: digoxin* | *€ 114* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: antithrombotic (DOAC)* | *€ 1,392* | (Farmacotherapeutisch Kompas, n.d.) |
| CAD treatment and control | € 1,759 | |
| *Control: 1x visit to the cardiologist + 2x visit to the GP per year* | *€ 194* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: beta-blockers / calcium antagonists* | *€ 103* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: statin* | *€ 70* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: antithrombotic* | *€ 1,392* | (Farmacotherapeutisch Kompas, n.d.) |
| HF - NYHA-I treatment and control | € 157 | |
| *Control: 1x visit to the GP per year* | *€ 41* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: ACE-inhibitors + Diuretics* | *€ 116* | (Farmacotherapeutisch Kompas, n.d.) |
| HF - NYHA-II treatment and control | € 198 | |
| *Control: 2x per year to the GP per year* | *€ 82* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: ACE-inhibitors + Diuretics* | *€ 116* | (Farmacotherapeutisch Kompas, n.d.) |
| HF - NYHA-III treatment and control | € 310 | |
| *Control: 1x visit to the cardiologist + 2x visit to the GP per year* | *€ 194* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: ACE-inhibitors + Diuretics* | *€ 116* | (Farmacotherapeutisch Kompas, n.d.) |
| HF - NYHA-IV treatment and control | € 1,143 | |
| *Control: 2x visit to the cardiologist + 2x visit to the GP per year* | *€ 306* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: ACE-inhibitors + Diuretics* | *€ 116* | (Farmacotherapeutisch Kompas, n.d.) |
| *Medication: SGLT2-inhibitors* | *€ 721* | (Farmacotherapeutisch Kompas, n.d.) |
| Mild CKD treatment and control | € 98 | |
| *Control: 1x visit to the GP per year* | *€ 41* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: ACE-inhibitor* | *€ 57* | (Farmacotherapeutisch Kompas, n.d.) |
| Moderate CKD treatment and control | € 972 | |
| *Control: 1x visit to the nephrologist + 2x visit to the GP per year* | *€ 194* | (Hakkaart-van Roijen et al., 2015) |
| *Medication: ACE-inhibitor* | *€ 57* | (Farmacotherapeutisch Kompas, n.d.) |

| | | |
|---|---|---|
| *Medication: SGLT2-inhibitors* | *€ 721* | (Farmacotherapeutisch Kompas, n.d.) |
| Severe CKD treatment and control | € 11,929 | (van Oosten et al., 2020) |
| ESRD treatment and control | € 11,929 | (van Oosten et al., 2020) |
| Prediabetes treatment and control (1x visit to the GP per year) | € 41 | (Hakkaart-van Roijen et al., 2015) |
| DM2 treatment and control | € 6,978 | (S. A. G. de Vries et al., 2023) |
| Cardioversion in persistent AF | € 236 | (Ringborg et al., 2008) |
| Ablation surgery in persistent AF | € 5,939 | (Ringborg et al., 2008) |
| Bypass surgery in CAD | € 13,132 | (ZiN, 2017) |
| Angioplasty in CAD | € 5,623 | (ZiN, 2017) |
| **RENAL REPLACEMENT THRAPY COSTS (ANNUALLY)** | | |
| **Description** | **Cost** | **Source** |
| Annual cost kidney dialysis (centre haemodialysis) | €113,152 | (Mohnen et al., 2019) |
| Kidney transplantation: Year 1 | € 99,951 | (Mohnen et al., 2019) |
| Kidney transplantation: Year 2 | € 34,769 | (Mohnen et al., 2019) |
| Annual cost kidney transplantation from year 3 onwards | € 23,666 | (Mohnen et al., 2019) |
| Annual cost conservative treatment (cost palliative care) | € 14,260 | (Gardiner et al., 2018) |
| **CARDIOVASCULAR EVENT COSTS** | | |
| **Description** | **Cost** | **Source** |
| Acute cost IS (recovered patients) | € 20,448 | (van Hulst et al., 2022) |
| Annual cost IS (recovered patients) | € 6,340 | (van Hulst et al., 2022) |
| Acute cost IS (not recovered patients) | € 47,139 | (van Hulst et al., 2022) |
| Annual cost IS (not recovered patients) | € 16,908 | (van Hulst et al., 2022) |
| Death IS | € 11,938 | (van Hulst et al., 2022) |
| Acute cost HS (recovered patients) | € 25,944 | (van Hulst et al., 2022) |
| Annual cost HS (recovered patients) | € 7,224 | (van Hulst et al., 2022) |
| Acute cost HS (not recovered patients) | € 47,139 | Assumption: same as acute IS |
| Annual cost HS (not recovered patients) | € 16,908 | Assumption: same as annual IS |
| Death HS | € 6,448 | (van Hulst et al., 2022) |
| Acute cost MI | € 5,362 | (van Hulst et al., 2022) |
| Annual cost MI | € 1,196 | (van Hulst et al., 2022) |
| Death MI | € 5,362 | Assumption: same as acute MI |
| Acute cost CA (recovered patients) | € 5,362 | Assumption: same as acute MI |
| Annual cost CA (recovered patients) | € 1,196 | Assumption: same as annual MI |
| Acute cost CA (not recovered patients) | € 5,362 | Assumption: same as acute MI |
| Annual cost CA (not recovered patients) | € 1,196 | Assumption: same as annual MI |
| Death CA | € 5,362 | Assumption: same as death MI |
| Death acute HF | € 5,704 | (Stevanovic et al., 2014) |
| TIA (acute cost) | € 3,057 | (Buisman et al., 2015) |
| TIA (annual treatment cost for those patients without treatment yet: 1 GP visit per year and antithrombotic) | € 1,433 | Assumption |

## 2.9. Discounting

People generally value future costs and effects less than current costs and effects. The value often diminishes the more distant in the future they occur (Attema et al., 2018). Hence, it is recommended to adjust the costs and effects for the time they occur, also known as discounting. Guidelines from the National Healthcare Institute of the Netherlands recommend using an annual discount rate of 4% for costs and 1.5% for effects (ZiN, 2016). In the health economic model, we implemented a continuous discount rate using the following formula:

$$PV_x = \frac{-X_0}{\log(1+r)} \cdot \left(\frac{1}{1+r}^{t_e} - \frac{1}{1+r}^{t_s}\right)$$

Where,

PV: Present value;

$X_0$: Cost or Effect in year 0 (start of the simulation);

r: Annual discount rate: 0.04 for costs and 0.015 for effects;

$t_e$: End time (in years);

$t_s$: Start time (in years).

## 2.10. Analyses

To compare the health economic impact of the screening strategy with usual care, we performed different types of analyses over a lifetime horizon. First, we performed a deterministic analysis, where we evaluated the DES model for the usual care strategy compared to the screening strategy, using parameter means and patient-level variation (i.e., stochastic uncertainty). Therefore, the patient characteristics of SBP, TC-level, HDL-level, eGFR, and ACR were different per individual. We also performed a deterministic scenario analysis, comparing usual care with an optimistic and pessimistic scenario for home-based screening (Table 31).

For the optimistic and pessimistic scenario, we decided to construct the scenarios based on the model inputs associated with participation throughout the screening process, the costs of the at-home tests, and the diagnostic performance of the at-home tests. The scenarios were constructed as follows: in the optimistic scenario, we assumed that the probability of participating in the screening process was increased by 10% compared to the standard screening strategy. The costs per individual for the AF-test and the questionnaire were decreased to €0.20. Furthermore, the sensitivity and specificity of the albuminuria test and the AF-test were set to the upper limit of the 95% confidence interval, as reported by van Mil et al. (2023) and Mol et al. (2020). The sensitivity and specificity of the questionnaire to detect CAD, HF, and DM2 were set to 100%. In the pessimistic scenario, we assumed that the probability of participating in the screening process was decreased by 10% compared to the standard screening strategy. The costs per individual for the AF-test and the questionnaire were increased to €2.00 each. The sensitivity and specificity of the albuminuria test and the AF-test were set at the lower limit of the 95% confidence interval. Furthermore, the diagnostic performance of the questionnaire was set to 90%. The diagnostic performance of extensive screening was maintained at 100%.

**Table 31.** Selected inputs base-case scenario, optimistic scenario, and pessimistic scenario.

| | Scenario | | |
|---|---|---|---|
| **Input** | **Base-Case** | **Optimistic** | **Pessimistic** |
| *Participation* | | | |
| Probability to participate Check@Home test | 59.4 % | 65.3 % | 53.5 % |
| Probability to participate follow-up test 1 | 92.8 % | 100.0 % | 83.5 % |
| Probability to participate follow-up test 2 | 92.8 % | 100.0 % | 83.5 % |
| Probability to participate extensive screening | 82.7 % | 91.0 % | 74.4 % |
| Probability to go to the GP after referral | 57.4 % | 63.1 % | 51.7 % |
| *Cost* | | | |
| Sending the invite + UCD per individual | € 3.82 | € 3.82 | € 3.82 |
| Sending back the UCD + analysis per individual | € 8.38 | € 8.38 | € 8.38 |
| Extensive screening per individual | € 53.80 | € 53.80 | € 53.80 |
| Happitech and questionnaire per individual | € 2.00 | € 0.40 | € 4.00 |
| *Diagnostic Performance* | | | |
| Sensitivity CKD (home test, UCD) | 96.6 % | 99.1 % | 91.5 % |
| Specificity CKD (home test, UCD) | 97.3 % | 98.8 % | 94.7 % |
| Sensitivity AF (home test, Happitech) | 98.1 % | 99.8 % | 93.4 % |
| Specificity AF (home test, Happitech) | 98.1 % | 99.8 % | 93.2 % |
| Sensitivity CAD, HF, DM2 (home test, questionnaire) | 95.0 % | 100 % | 90 % |
| Specificity CAD, HF, DM2 (home test, questionnaire) | 95.0 % | 100 % | 90 % |
| Sensitivity extensive screening | 100.0 % | 100 % | 100 % |
| Specificity extensive screening | 100.0 % | 100 % | 100 % |

To determine the stability of the results, we evaluated the DES model for 200,000 individuals. Subsequently, we took 1,000 random samples of the incremental costs and incremental QALYs for different numbers of individuals. Next, we determined the mean per sample and calculated the 2.5$^{th}$ and 97.5$^{th}$ percentile values (Appendix 9). Figure 6 and 7 present the convergence plots of the incremental costs and incremental QALYs, including the mean, lower (2.5$^{th}$ percentile) and upper bound (97.5$^{th}$ percentile). Figure 6 and 7 show that around 100,000 individuals must be simulated, to get relatively stable mean incremental costs and QALYs. In the deterministic analysis we decided to evaluate the DES model for 200,000 individuals.

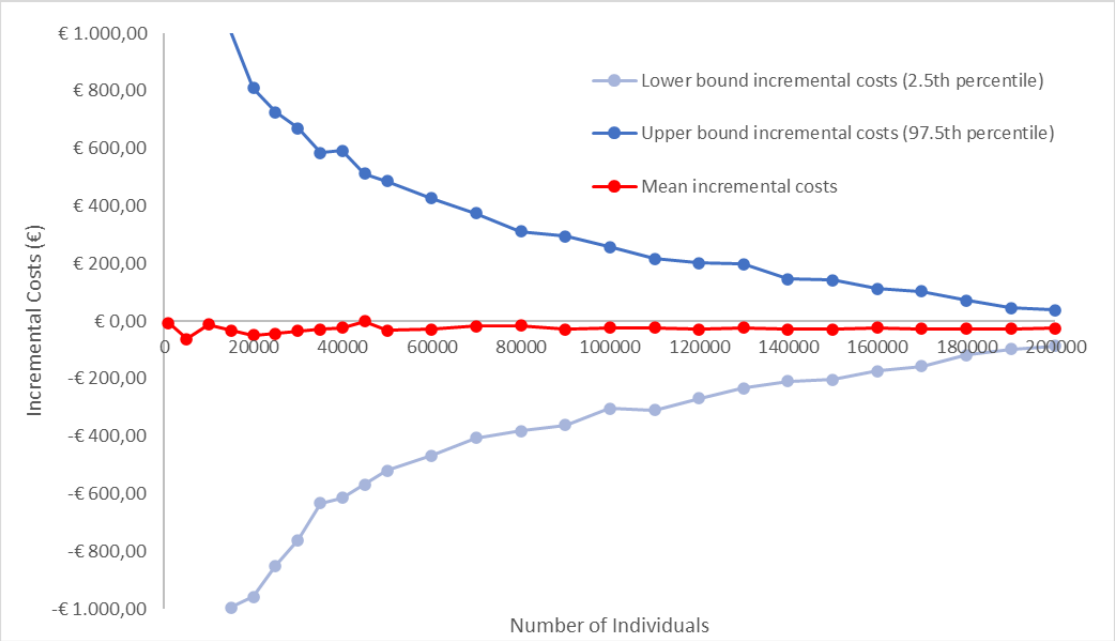



**Figure 6.** Convergence plot of the incremental costs

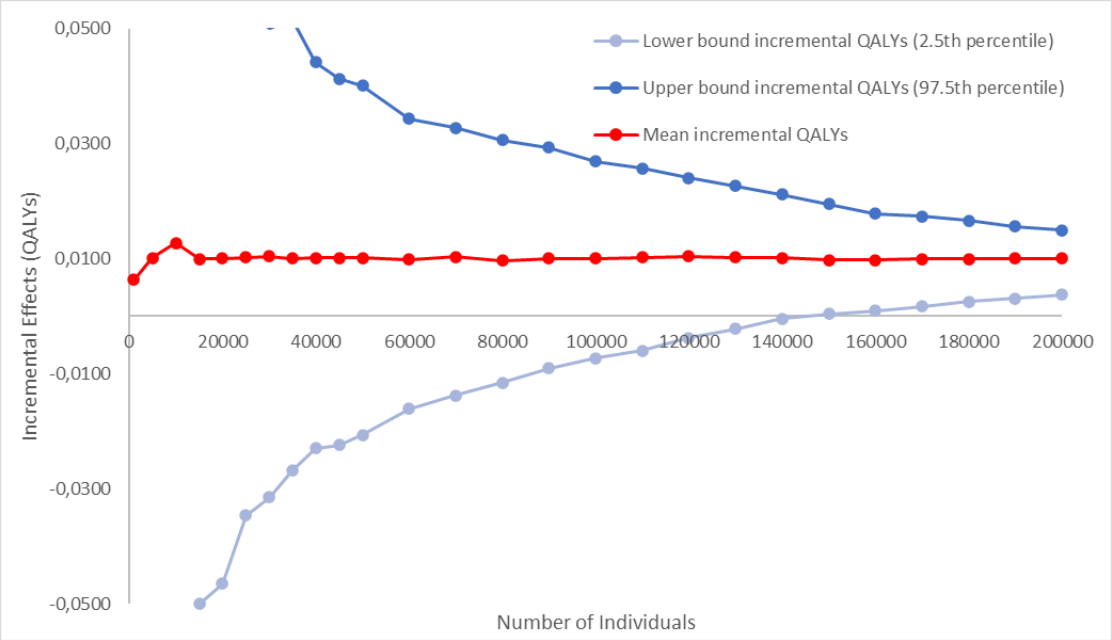



**Figure 7.** Convergence plot of the incremental effects (QALYs)

According to good research practices and modeling guidelines, parameter uncertainty should be accounted for in a probabilistic sensitivity analysis (PSA) to calculate the expected health economic outcomes and express the uncertainty in these estimates (Briggs et al., 2012; ZiN, 2016). Appendix 8 provides an overview of the distributions used for parameter uncertainty. In the PSA, we evaluated the DES model 200 times using Monte Carlo Sampling for 50,000 individuals. In addition to the primary and secondary outcomes, an incremental cost-effectiveness plane and cost-effectiveness acceptability curve were presented. The decisions made in the PSA are presented in Table 32.

**Table 32.** List of PSA decision

| Decision | Description |
|---|---|
| **1.** | To populate the model at model initiation, we used several input data from sources such as CBS, the Ministry of Health, Welfare, and Sport, the Nivel Care Registry, the Dutch Heart Foundation, the Kidney Foundation, and the Diabetes Fund. This applies to the parameters used for setting the individual's gender, age, smoking status, and disease prevalence (for AF, CAD, HF, and DM2). We assumed that these organizations have complete data for the Dutch population, so there is no parameter uncertainty. Hence, these parameters were fixed in the PSA. |
| **2.** | For the remaining parameters used at model initiation (i.e., from other sources than named at decision 1), we did consider parameter uncertainty. For the stage distributions of AF, HF, and CKD, we used a Dirichlet distribution. The alpha parameter in the Dirichlet distribution was set equal to the total number of patients per disease stage (Chiang et al., 2012; Norhammar et al., 2023; Leemrijse et al., 2021). The prevalence rates for CKD (van Blijderveen et al., 2014) and Prediabetes (van Herpt et al., 2020) were assessed using a Beta distribution. The two shape parameters in the Beta distribution were estimated using the Method of Moments with given mean and by using the 95% confidence interval. Where $SE = (\text{Percentile}_{97.5\text{th}} - \text{Percentile}_{2.5\text{th}})/(2 \cdot 1.96)$. |

| | |
|---|---|
| **3.** | In the diagnostic and treatment pathway, we made several assumptions about the tests and scans used to diagnose patients (Table 5). Assumptions related to the usage of diagnostic resources were assumed to be fixed for all PSA runs. For instance, we assumed that 100% of the suspected AF patients get a standard ECG at the GP. We fixed this in all PSA runs. |
| **4.** | In the diagnostic and treatment pathway, we also made assumptions about the interventions provided to treat patients (e.g., medical therapy or surgical interventions). Probabilities associated with receiving cardioversion, ablation surgery, angioplasty, and bypass surgery were assessed using a Beta distribution, with standard error equal to 20% of the mean probability. The Method of Moments was used to estimate the two shape parameters of the Beta distribution. |
| **5.** | In addition to surgical interventions, patients were assigned an annual treatment plan consisting of medical therapy and control visits at the GP or hospital. In the PSA, we assumed that the annual costs dedicated to medical therapy (e.g., calcium antagonists for AF patients) were fixed for every patient in all PSA runs.<br>The number of control visits were originally based on NHG guidelines. In the PSA, we assessed the number of control visits using a Gamma distribution (no negative visits), where the standard error was equal to 20% of the mean number of visits (Table 5). The Method of Moments was used to estimate the shape and scale parameter of the Gamma distribution. |
| **6.** | For the annual treatment costs of severe CKD and kidney failure, we used aggregated costs reported by van Oosten et al. (2020). In the health economic analysis of the THOMAS study, the costs from van Oosten et al. (2020) were also used (Pouwels et al., 2023). In our PSA, we used the same Gamma distribution as reported in the THOMAS study, with given mean and standard error. |
| **7.** | For the annual treatment costs of DM2, we used the aggregated costs reported by de Vries et al. (2023). No uncertainty around the mean costs was expressed. Therefore, to assess the costs associated with DM2 treatment, a Gamma distribution was applied, with a standard error of 20% of the mean aggregated costs. |
| **8.** | For the annual costs of kidney dialysis and kidney transplantation, we used the aggregated costs reported by Mohnen et al. (2019). To assess the costs for kidney dialysis and kidney transplantation, we used a Gamma distribution with given mean and standard error. |
| **9.** | The acute and annual costs associated with CVD-events, were aggregated costs. The uncertainty around the mean costs was not expressed. Therefore, we assessed the acute and annual costs of CVD-events using a Gamma distribution, with given mean and standard error equal to 20% of the mean costs. |
| **10.** | Utility values (Table 29) were assessed by using a Beta distribution. The Method of Moments was used to calculate the two shape parameters (i.e., α and β). To ensure that the utility of a diseased individual is lower than the utility of a healthy individual, we capped all utilities of disease status to the utility of a healthy status (i.e., minimum function). |
| **11.** | To assess hazard ratios and relative risks, a Log-Normal distribution was used with given mean and 95% confidence interval, where $\text{SE} = (\ln(\text{Percentile}_{97.5\text{th}}) - \ln(\text{Percentile}_{2.5\text{th}}))/(2 \cdot 1.96)$. |
| **12.** | Probabilities associated with progression were reflected using a Beta distribution. For the progression probabilities of AF and HF, we used data from cohort studies (Holmqvist et al., 2015; Packer et al., 2015). Here, the α was set equal to the number of progression events, and the β was set equal to the study population minus the number of progression events. For the progression probabilities of CKD, Elbasha et al. (2017) provided the α and β. To assess the progression from prediabetes to DM2 (Table 19), a Beta distribution was applied, using the mean and 95% confidence interval from (van Herpt et al., 2020). Where $SE = (\text{Percentile}_{97.5\text{th}} - \text{Percentile}_{2.5\text{th}})/(2 \cdot 1.96)$. |
| **13.** | To assess the period and lifetime risks of developing AF, CKD, and DM2, a Beta distribution was used with the given mean and 95% confidence intervals from the cohort studies |

| | |
|---|---|
| | (Heeringa et al., 2006; Inker et al., 2015; Ligthart et al., 2016). We have ensured that the period risks further into the future cannot be lower than the risks before. For example, it cannot be the case that the risk period is higher at 5 years than at 10 years.<br>For the period and lifetime risks of developing CAD and HF, no uncertainty (e.g., 95% confidence interval) was expressed (Bleumink et al., 2004; Nivel, 2022). Instead, we assumed that the period and lifetime risk of CAD and HF was normally distributed with a given mean and standard error equal to 20% of the mean probability. To do this, we drew one uncertainty factor from the normal distribution, N(1,0.2). The same factor was applied to all periodic risks. For example, when the factor is 0.95, all period risk are multiplied with 0.95. Indicating that all period risk are reduced by 5%. |
| **14.** | The probabilities to determine the risk of experiencing a TIA (Table 26) and the risk to die from other causes (Table 27) came from the Nivel Care Registry (Nivel, 2022) and the Dutch National Statistics (CBS, 2023c). We assumed that these organizations have complete data about the Dutch population, and therefore, there is no uncertainty in the probabilities for risks of TIA and background mortality. |
| **15.** | To assess the probabilities which CVD-event occurs (Table 23), a multivariate Beta distribution (i.e., Dirichlet distribution) was used. The alpha parameter of the Dirichlet distribution was set equal to the total number of deaths and hospitalization events reported in Table 23. |
| **16.** | To assess the probabilities of a fatal CVD-event (Table 24), we used data from the Dutch Heart Association (Hartstichting, 2021) and Zijlstra et al. (2016). The Heart Association did not provide the original outcomes of the number of fatal events in the study population. Therefore, to assess the probabilities of a fatal IS, HS, and MI, we used a Beta distribution with a standard error equal to 20% of the mean probability. Zijlstra et al. (2016) reported the number of fatal and non-fatal CA events in six regions in the Netherlands. To assess the probability of a fatal CA event, we used a Beta distribution, where $\alpha$ was set equal to the number of fatal CA events, and $\beta$ was set equal to the study population minus the number of fatal CA events. |
| **17.** | The probabilities associated with recovering from a CVD-event (Table 24) and the 5-year mortality probabilities after a CVD-event (Table 25) were assumed to follow a Beta distribution, with a standard error equal to 20% of the mean probability. |
| **18.** | The life expectancy of dialysis patients and kidney transplantation patients (Table 18) was assumed to be normally distributed (truncated: no negative life expectancy), with a standard error equal to 20% of the mean life expectancy. |
| **19.** | Screening inputs were primarily based on the results from the THOMAS study (van Mil et al., 2023). The participation probabilities were assumed to follow a Beta distribution, where $\alpha$ was set to the number of participants and $\beta$ to the study population minus the number of participants. The sensitivity and specificity of the albuminuria test and the AF-test were assumed to follow a Beta distribution. The sensitivity and specificity of the questionnaire were assumed to follow a truncated normal distribution with a mean of 0.95 and a standard error of 0.025. |

# 3. Assumption Impact Analysis

In the previous Chapter, we introduced several structural assumptions in the health economic model for Check@Home. In this Chapter, we aimed to evaluate the impact of two assumptions on the results of the health economic model. The two assumptions were selected because we could not substantiate the assumptions based on evidence from the literature or verify them with clinical experts. We evaluated the health economic model for two extreme scenarios for the two assumptions, deliberately pushing the model's boundaries with extreme inputs. Then, we assessed how sensitive the model's outputs were to the inputs used. Through this process, we sought to provide insights into the potential implications of the assumption on the outcomes of the model.

The first assumption whose impact we wanted to evaluate was: "*For the diseases AF, HF, and CKD, we assumed that the stage distribution among the undiagnosed population is 67.7% in the first disease stage, and 33.3% in the second disease stage.*". In the first extreme scenario, we set the stage distribution in the undiagnosed population to 100% in the first disease stage and 0% in the other disease stages. In contrast, in the second extreme scenario, 50% of the undiagnosed population is in the first disease stage, and 50% is in the second disease stage. The primary and secondary outcomes of both scenarios for the usual care strategy and screening strategy are presented in Table 33 (n = 100,000 individuals).

**Table 33.** Primary and secondary outcomes scenario 1 and 2: stage distribution in the undiagnosed population.

| | **Scenario 1: 100-0%** | | **Scenario 2: 50-50%** | |
|---|---|---|---|---|
| | **Usual Care** | **Screening** | **Usual Care** | **Screening** |
| **Primary Outcomes** | | | | |
| Mean costs per individual | € 30,716.76 | € 31,112.84 (+ €396.08) | € 32,016.83 | € 31,995.79 (- €21.04) |
| Mean LYs per individual | 22.001 | 22.013 (+ 0.012) | 21.975 | 21.979 (+ 0.004) |
| Mean QALYs per individual | 14.613 | 14.620 (+ 0.007) | 14.584 | 14.586 (+ 0.002) |
| Cost per QALY (ICUR) gained compared to usual care | | €52,851 (Not Cost-Effective) | | - €10,461 (Dominant) |
| **Secondary Outcomes** | | | | |
| Number of new diagnoses through screening | | 4313 (4.3%) | | 4313 (4.3%) |
| Number of individual experiencing a CVD complication | 28227 (28.2 %) | 28091 (28.1 %) | 28317 (28.3 %) | 28161 (28.2 %) |
| Number of individuals who progressed to kidney failure | 3980 (4.0 %) | 3955 (4.0 %) | 4258 (4.3 %) | 4178 (4.2 %) |
| *Of whom received conservative therapy (palliative care)* | *1186 (29.8%)* | *1136 (28.7%)* | *1220 (28.7%)* | *1169 (28.0%)* |
| *Of whom received RRT* | *2794 (70.2%)* | *2819 (71.3%)* | *3038 (71.3%)* | *3009 (72.0%)* |
| Mean time until CVD complication occurs (years) | 17.65 | 17.71 (+ 0.06) | 17.61 | 17.68 (+ 0.07) |
| Mean time until CKD patients progress to kidney failure (years) | 17.83 | 17.63 (- 0.20) | 17.07 | 17.29 (+ 0.22) |

When we compare the primary outcomes in the two scenarios from Table 33, we observe that the costs per patient are lower in the first scenario than in the second scenario. This is the case for both the usual care and screening strategy. Additionally, the healthy effects per patient (i.e., both LYs and QALYs) are higher in the first scenario than in the second scenario. These outcomes are as expected because, in the second scenario, there is a larger group of individuals in more advanced disease stages than in the first scenario. When individuals get diagnosed in a more advanced disease stage, they receive more expensive treatments (i.e., more control visits and more medical therapy) than those diagnosed in a less advanced disease stage. As a result, the costs per patient in the second scenario are higher than in the first scenario. Furthermore, patients in more advanced disease stages have a higher risk of experiencing a CVD complication, and more advanced CKD patients are more likely to progress to kidney failure. This is also confirmed by the secondary outcomes in Table 33, where the number of CVD complications and patients who progress to kidney failure are higher in the second scenario than in the first scenario (for both usual care and screening). Moreover, patients in more advanced disease stages have a lower utility value than those in less advanced disease stages. As a result, the QALYs per patient are lower in the second scenario than in the first scenario.

In the first scenario, screening compared to usual care results in an ICUR of €52,851. Compared to a WTP of €20,000 per QALY, the ICUR implies that screening is not cost-effective. In contrast, in the second scenario, the ICUR is - €10,461, meaning that screening dominates usual care (i.e., screening leads to lower costs and higher QALYs per patient). The difference in the ICURs between the two scenarios (and the conclusion that comes with it) indicates that the assumption about the stage distribution among the undiagnosed population has a significant impact on the outcomes of the health economic model. The difference between the ICURs highlights the necessity of making the right choices for the assumption. Therefore, in a future health economic model, the assumption should be verified among clinical experts or supported by evidence from empirical studies.

The second assumption whose impact we wanted to evaluate was: "*Undiagnosed patients were classified based on their disease stage into low, middle, high, and very-high stages. The probabilities to get diagnosed (i.e., visit the GP) were 10%, 50%, 85%, and 100%, respectively.".* The two extreme scenarios evaluated are presented in Table 34.

**Table 34.** Two extreme scenarios: probabilities to visit the GP in low, middle, high, and very-high stages.

| | **Scenario 3** | **Scenario 4** |
|---|---|---|
| **Low stages** | 0% | 30% |
| **Middel stages** | 30% | 75% |
| **High stages** | 75% | 95% |
| **Very-high stages** | 100% | 100% |

The primary and secondary outcomes of the third and fourth scenario are presented in Table 35. From the primary outcomes in Table 35, we observe that the costs and the health effects (i.e., LYs and QALYs) per patient are lower in scenario 3 than in scenario 4. These outcomes are as expected because in scenario 4 undiagnosed patients are more likely to get diagnosed in early disease stages. As a result, a disease diagnosis occurs earlier in scenario 4 than in scenario 3. As patients get diagnosed earlier, they also start treatment earlier. Therefore, treatment costs are incurred earlier, leading to the higher costs per patient in scenario 4. Furthermore, as undiagnosed

individuals are diagnosed and treated earlier in scenario 4, they experience a lower risk of experiencing a CVD complication. Consequently, the number of individuals experiencing a CVD complication is also lower in scenario 4 than in scenario 3 (28298 vs 27934 in the screening strategy). Also, fewer CKD patients progress to kidney failure in scenario 4 than in scenario 3 (4215 vs 3899 in the screening strategy). The progression to kidney failure also occurs later in scenario 4 than in scenario 3 (17.18 years vs 17.69 years in the screening strategy).

The ICUR is equal to - €421 in scenario 3 and €523,363 in scenario 4. Consequently, in scenario 3, screening dominates usual care. In scenario 4, screening is not cost-effective compared to a WTP threshold of €20,000. The difference in ICURs between the two scenarios (and the conclusion that comes with it) emphasizes that the assumption about the probability of getting diagnosed significantly impacts the outcome of the health economic model. As with the first assumption, in a future health economic model, this assumption must also be verified by clinical experts or supported by evidence from empirical studies.

**Table 35.** Primary and secondary outcomes scenario 3 and 4: probability to get diagnosed per stage category.

| | **Scenario 3: 0-30-75-100%** | | **Scenario 4: 30-75-95-100%** | |
|---|---|---|---|---|
| | **Usual Care** | **Screening** | **Usual Care** | **Screening** |
| **Primary Outcomes** | | | | |
| Mean Costs per individual | €31,283.08 | €31,273.82 (- €9.26) | €31,771.25 | €31,876.44 (+ €105.19) |
| Mean LYs per individual | 21.944 | 21.978 (+ 0.034) | 22.012 | 22.023 (+ 0.011) |
| Mean QALYs per individual | 14.582 | 14.604 (+ 0.022) | 14.597 | 14.597 (+ 0.000) |
| Cost per QALY (ICUR) gained compared to usual care | | - €421 (Dominant) | | €523,363 (Not Cost-Effective) |
| **Secondary Outcomes** | | | | |
| Number of new diagnoses through screening | | 4333 (4.3%) | | 4333 (4.3%) |
| Number of individual experiencing a CVD complication | 28458 (28.5%) | 28298 (28.3%) | 27967 (28.0%) | 27934 (27.9%) |
| Number of individuals who progressed to kidney failure | 4296 (4.3%) | 4215 (4.2%) | 3922 (3.9%) | 3899 (3.9%) |
| *Of whom received conservative therapy (palliative care)* | 1250 (29.1%) | 1201 (28.5%) | 1122 (28.6%) | 1084 (27.8%) |
| *Of whom received RRT* | 3046 (70.9%) | 3014 (71.5%) | 2800 (71.4%) | 2815 (72.2%) |
| Mean time until CVD complication occurs (years) | 17.42 | 17.47 (+ 0.05) | 17.66 | 17.67 (+ 0.01) |
| Mean time until CKD patients progress to kidney failure (years) | 17.18 | 17.18 (+ 0.00) | 17.53 | 17.69 (+0.16) |

In addition to the two selected assumptions, it would have been interesting to evaluate the impact of multiple other assumptions. However, due to time constraints, in this master thesis we decided to only evaluate the impact of the two selected assumptions.

# 4. Results Deterministic Analysis

This Chapter presents the results from the deterministic analysis. The primary and secondary outcomes of the usual care strategy and the screening strategy are presented in Table 36. When we compare usual care with screening in a base-case scenario, we observe a decrease in the mean costs per individual (- €25.13) and an increase in health effects per individual (+ 0.010 QALYs and + 0.014 life years), resulting in an ICUR of - €2,519.48. The ICUR implies that screening is dominant and cost-saving compared to usual care.

On an individual level, the incremental costs and effects seem marginal. To put the outcomes in perspective, we also evaluate the health economic impact on a population level. The total target population (i.e., 50-75 year-olds in the Netherlands) was 5,662,163 people in 2021 (CBS, 2021). The results from the 200,000 individuals show that the screening strategy, in total, saves €5,027,329 and yields 1995 QALYs and 2587 LYs, compared to the usual care strategy. Consequently, in the total target population, the screening strategy saves €142,327,781 and yields 56,491 QALYS and 73,235 LYs compared to usual care.

Secondary outcomes show that 8626 individuals (i.e., 4.3%) are diagnosed through screening. Furthermore, in usual care, we observe 56,602 CVD complications (i.e., 2830 CVD complications per 10,000 individuals) compared to 56,321 CVD complications in the screening strategy (i.e., 2816 CVD complications per 10,000 individuals). This is equal to a reduction of 0.5% in CVD complications. The mean time until a CVD complication occurs increased from 17.59 years in usual care to 17.61 years in the screening strategy (i.e., on average, a CVD complication occurs 0.02 years later).

Moreover, comparing usual care with screening in a base-case scenario, the number of CKD patients who progress to kidney failure reduced by 0.5% (i.e., from 408 to 406 kidney failure patients per 10,000 individuals). Of the patients who progressed to kidney failure, in the screening strategy, there were proportionally fewer patients who received RRT (71.6% vs. 72.1% in usual care) and more conservative therapy (28.4% vs. 27.9% in usual care). Conservative therapy is only offered to patients older than 85 years. The fact that more kidney failure patients receive conservative therapy in the screening strategy seems to indicate that patients develop kidney failure at an older age. This is confirmed by the secondary outcomes, which show that the mean time until CKD patients progress to kidney failure increased from 17.24 years in the usual care strategy to 17.44 years in the screening strategy (i.e., on average, CKD patients progress to kidney failure 0.20 years later).

When we compare usual care with screening in an optimistic scenario, we observe a decrease in mean costs per individual (- €2.20) and an increase in effects (+ 0.021 QALYs and + 0.035 life years), resulting in an ICUR of - €98.34. The ICUR implies that screening in an optimistic scenario is dominant and cost-saving compared to usual care.

The proportion of individuals diagnosed through screening in an optimistic scenario is 6.6%. Furthermore, when we compare usual care with screening in an optimistic scenario, the number of CVD complications is reduced by 0.5%, and the mean time until a CVD complication occurs increases by 0.08 years. Remarkably, the number of CVD complications in the optimistic screening strategy (i.e., 56,340 CVD complications) is higher than in the base-case scenario (i.e., 56,321 CVD complications). In Chapter 6, we discuss possible causes for this result.

In an optimistic scenario for screening, the number of individuals who progress to kidney failure is reduced by 0.8% compared to usual care. The average time CKD patients progress to kidney failure increased from 17.24 years in usual care to 17.63 years in screening (i.e., an increase of 0.39 years). Moreover, fewer kidney failure patients receive RRT in the optimistic scenario compared to the base-case scenario for screening.

Finally, when we compare usual care with screening in a pessimistic scenario, we observe a decrease in mean costs per individual (- €5.80) and an increase in health effects (+ 0.002 QALYs and + 0.001 LYs), resulting in an ICUR of - €4,488.79. The ICUR implies that screening in a pessimistic scenario is dominant and cost-saving compared to usual care.

The proportion of individuals diagnosed through screening in a pessimistic scenario is 2.7%. When we compare usual care to screening in a pessimistic scenario, the number of CVD complications is reduced by 0.2%, and the mean time until a CVD complication occurs increases from 17.59 years to 17.60 years.

Furthermore, in a pessimistic scenario, the number of individuals progressing to kidney failure reduced marginally by 0.1%. The average time until CKD patients progress to kidney failure remained at 17.24 years. Remarkably, proportionally more kidney failure patients receive RRT in the pessimistic scenario than in the usual care strategy. In Chapter 6, we discuss possible explanations for this result.

**Table 36.** Results deterministic analysis (n = 200,000).

| | **Usual Care** | | **Screening** Base-Case Scenario | | **Screening** Optimistic Scenario | | **Screening** Pessimistic Scenario | |
|---|---|---|---|---|---|---|---|---|
| **Primary Outcomes** | | | | | | | | |
| | *Value* | *%* | *Value* | *+/-* | *Value* | *+/-* | *Value* | *+/-* |
| Mean Costs per individual | €31,600.20 | | €31,575.07 | -€25.13 | €31,598.15 | -€2.20 | €31,594.40 | -€5.80 |
| Mean LYs per individual | 21.944 | | 21.957 | +0.014 | 21.978 | +0.035 | 21.945 | +0.001 |
| Mean QALYs per individual | 14.569 | | 14.579 | +0.010 | 14.590 | +0.021 | 14.571 | +0.002 |
| Cost per QALY (ICUR) gained compared to usual care | | | -€2,519.48 (Dominant) | | -€98.34 (Dominant) | | -€4,488.79 (Dominant) | |
| **Secondary Outcomes** | | | | | | | | |
| | *Value* | *%* | *Value* | *+/-/%* | *Value* | *+/-/%* | *Value* | *+/-/%* |
| Number of new diagnoses through screening | - | - | 8626 | 4.3% | 13156 | 6.6% | 5340 | 2.7% |
| Number of individual experiencing a CVD complication | 56602 | 28.3% | 56321 | 28.2% *(- 0.5%)* | 56340 | 28.2% *(- 0.5%)* | 56461 | 28.2% *(-0.2%)* |
| Number of individuals who progress to kidney failure | 8169 | 4.1% | 8128 | 4.1% *(- 0.5%)* | 8101 | 4.1% *(- 0.8%)* | 8161 | 4.1% *(-0.1%)* |
| *Of whom receive conservative therapy (palliative care)* | *2276* | *27.9%* | *2307* | *28.4%* | *2353* | *29.0%* | *2240* | 27.4% |
| *Of whom receive RRT* | *5893* | *72.1%* | *5821* | *71.6%* | *5748* | *71.0%* | *5921* | 72.6% |
| Mean time until CVD complication occurs (years) | 17.59 | | 17.61 | +0.02 | 17.67 | +0.08 | 17.60 | +0.01 |
| Mean time until CKD patients progress to kidney failure (years) | 17.24 | | 17.44 | +0.20 | 17.63 | +0.39 | 17.24 | +0.00 |
| **Diagnosed vs. Undiagnosed** (Proportion at the end of the time horizon) | | | | | | | | |
| Diagnosed | 66.0% | | 67.7% | | 68.9% | | 67.4% | |
| Undiagnosed | 34.0% | | 32.3% | | 31.1% | | 32.6% | |

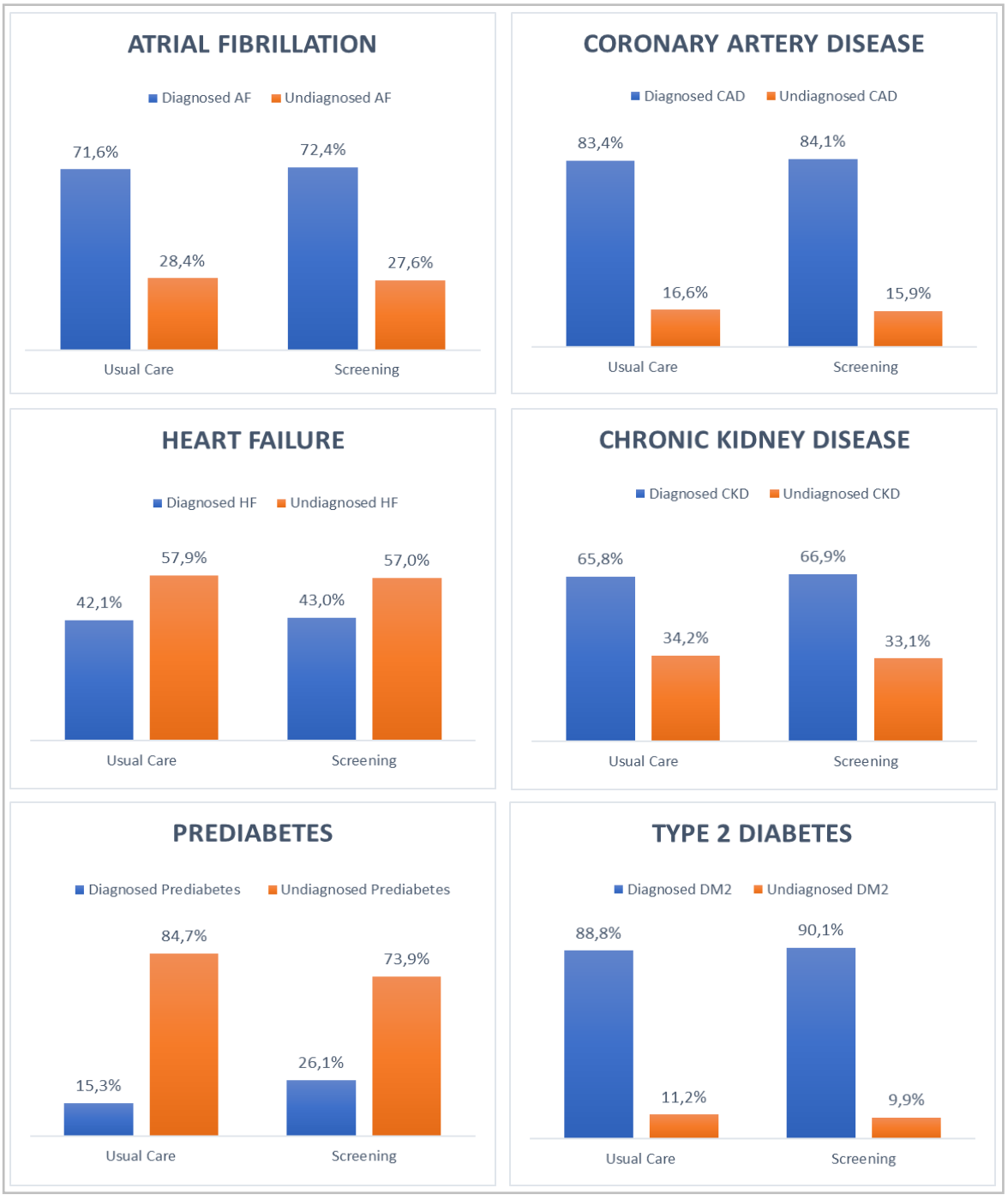



**Figure 8.** Distribution diagnosed and undiagnosed in the usual care and screening strategy for the five disease domains

In addition to the primary and secondary outcomes, we examined the disease status per individual at the end of the simulation (Appendix 10). Figure 8 presents the ratio of diagnosed-undiagnosed in the usual care and screening strategy for all five disease domains (diabetes is divided into prediabetes and DM2). The ratios in Figure 8 are at the end of the simulation. When we study Figure 8, we can observe that the group "diagnosed" (blue bar) is larger in the screening strategy than usual care for all disease domains. The group "undiagnosed" (orange bar), on the other hand, is smaller in the screening strategy compared to usual care. Moreover, we can see that in HF and prediabetes, the "undiagnosed" group is larger than the "diagnosed" group.

Finally, Figure 9 presents the stage distribution of AF, HF, CKD, and DM2 at the end of the simulation lifetime for the usual care and screening strategy among diagnosed patients. The disease domain CAD was not presented in the figure, as no stages were defined. Figure 9 shows that diagnosed HF, CKD, and DM2 patients were generally in less advanced disease stages at the end of the simulation model. For example, the HF stage distribution showed that in the screening strategy, more patients were in NYHA-I and NYHA-II (i.e., 42.8% combined) compared to the usual care strategy (i.e., 41.6% combined). In contrast, in the screening strategy, fewer people were in NYHA-III and NYHA-IV (i.e., 57.2% combined) compared to usual care (i.e., 58.4% combined). Similar results were observed in CKD and DM2. Figure 9 also shows that, in the screening strategy, there were proportionally more AF patients with permanent AF (i.e., highest disease stage) than paroxysmal and persistent AF. This can be explained by the fact that we assumed that treatment does not affect AF progression (see Chapter 2).

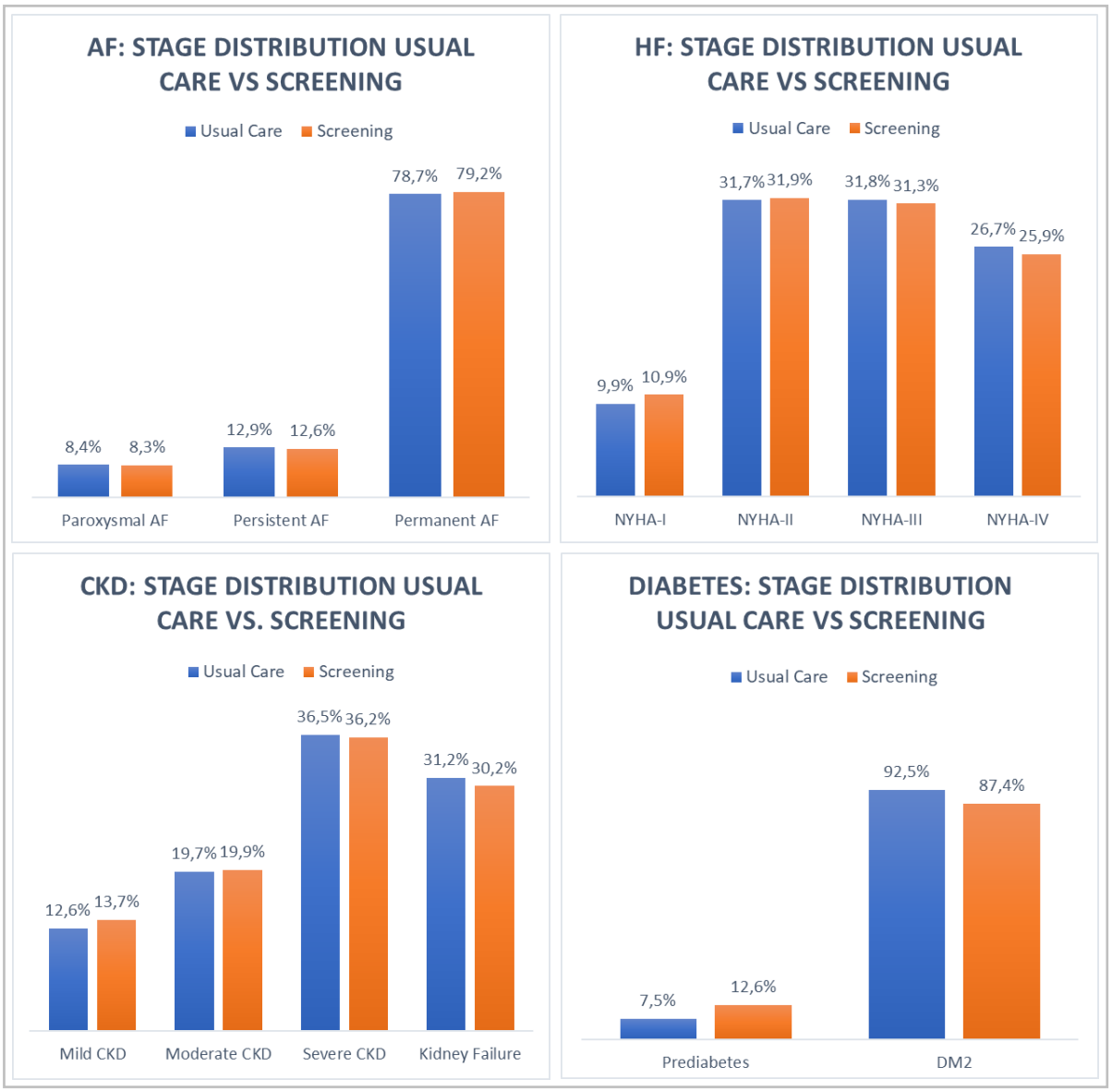



**Figure 9.** AF, HF, CKD, DM2 stage distribution (among diagnosed patients) at the end of the simulation for the usual care and base-case screening strategy.

# 5. Results Probabilistic Analysis

The mean results in the PSA are presented in Table 37. On average, when we compare the screening strategy with usual care, we observe a decrease in costs per individual (- €1.68) and an increase in health effects (+ 0.010 QALYs and + 0.015 LYs), resulting in an ICUR of - €173.86. The ICUR implies that, on average, screening, compared to usual care, is cost-saving. Secondary outcomes in Table 37 show that, on average, screening leads to better patient outcomes. In the screening strategy, fewer CVD complications occur (i.e., a reduction of 0.5%) than in the usual care strategy. Furthermore, fewer CKD patients progress to kidney failure (i.e., a reduction of 1.2%) than in the usual care strategy. Of the patients with kidney failure, fewer receive RRT in the screening strategy than usual care. Moreover, the mean time until a CVD complication occurs and the mean time until progression to kidney failure is later in the screening strategy than in usual care.

**Table 37.** Results PSA: mean and 95% confidence interval (200 runs and 50,000 individuals)

| | **Usual Care** | | **Screening** | |
|---|---|---|---|---|
| **Primary Outcomes** | | | | |
| | *Value* | | *Value* | *+/-* |
| Mean Costs per individual | €31,857.77<br>(95% CI: €27,375.27 - €36,792.70) | | €31,856.27<br>(95% CI: €27,267.75 - €36,793.92) | -€1.68 |
| Mean LYs per individual | 21.939<br>(95% CI: 21.760 – 22.117) | | 21.954<br>(95% CI: 21.769 – 22.117) | +0.015 |
| Mean QALYs per individual | 12.904<br>(95% CI: 5.303 – 15.988) | | 12.914<br>(95% CI: 5.302 – 16.037) | +0.010 |
| Cost per QALY gained compared to usual care | | | - €173.86<br>(Dominant) | |
| **Secondary Outcomes** | | | | |
| | *Value* | *%* | *Value* | *%/+/-* |
| Number of new diagnoses through screening | | | 2161<br>(95% CI: 1732 - 2623) | 4.3% |
| Number of CVD complications | 14,071<br>(95% CI: 13,580 – 14,624) | 28.1 % | 13,999<br>(95% CI: 13,516 - 14,499) | 28.0%<br>(-0.5%) |
| Number of individuals who progress to kidney failure | 2047<br>(95% CI: 1584 - 2662) | 4.1 % | 2021<br>(95% CI: 1537 - 2617) | 4.0%<br>(-1.2%) |
| *Of whom receive conservative therapy (palliative care)* | *571*<br>*(95% CI: 447 - 701)* | *27.9%* | *570*<br>*(95% CI: 447 - 713)* | *28.2%* |
| *Of whom receive RRT* | *1476*<br>*(95% CI: 1136 - 1962)* | *72.1%* | *1452*<br>*(95% CI: 1090 - 1905)* | *71.8%* |
| Mean time until CVD complication occurs (yr.) | 17.61<br>(95% CI: 17.41 – 17.78) | | 17.64<br>(95% CI: 17.42 – 17.82) | + 0.03 |
| Mean time until CKD patients progress to kidney failure (yr.) | 17.36<br>(95% CI: 16.67 – 17.97) | | 17.47<br>(95% CI: 16.89 – 18.08) | + 0.11 |

Figure 10 presents the increment cost-effectiveness plane. The red dots represent the incremental outcomes of the different PSA runs. The blue dot indicates the mean cost-effectiveness over the 200 runs. The dashed line presents the WTP threshold of €20,000 per QALY. Furthermore, Figure 11 shows the cost-effectiveness acceptability curve. The curve shows the probability of screening being cost-effective against different WTP thresholds. From Figure 11, we observe that at a WTP threshold of €20,000 per QALY, there is a 65.5% probability of screening being cost-effective. When the WTP threshold is much higher, €100,000, for example, there is a 72.5% probability of screening being cost-effective.

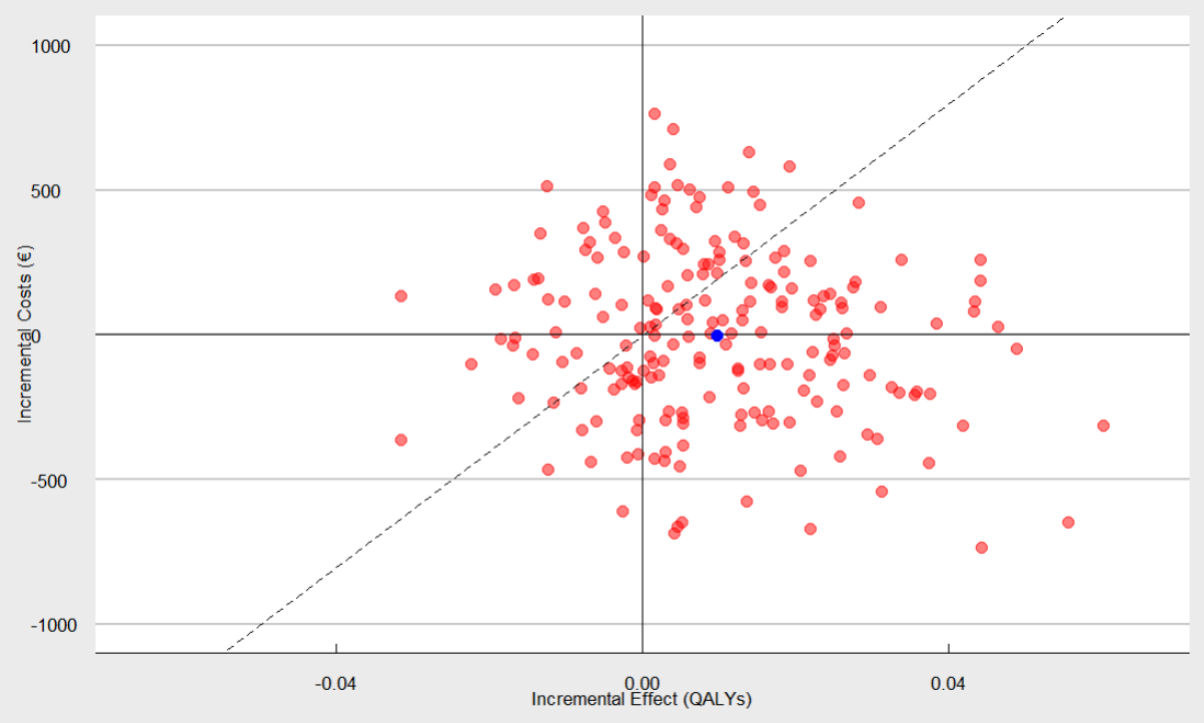



**Figure 10.** Incremental Cost-Effectiveness Plane: usual care vs. screening. Dashed-line (- -) represents the WTP-line for €20,000.

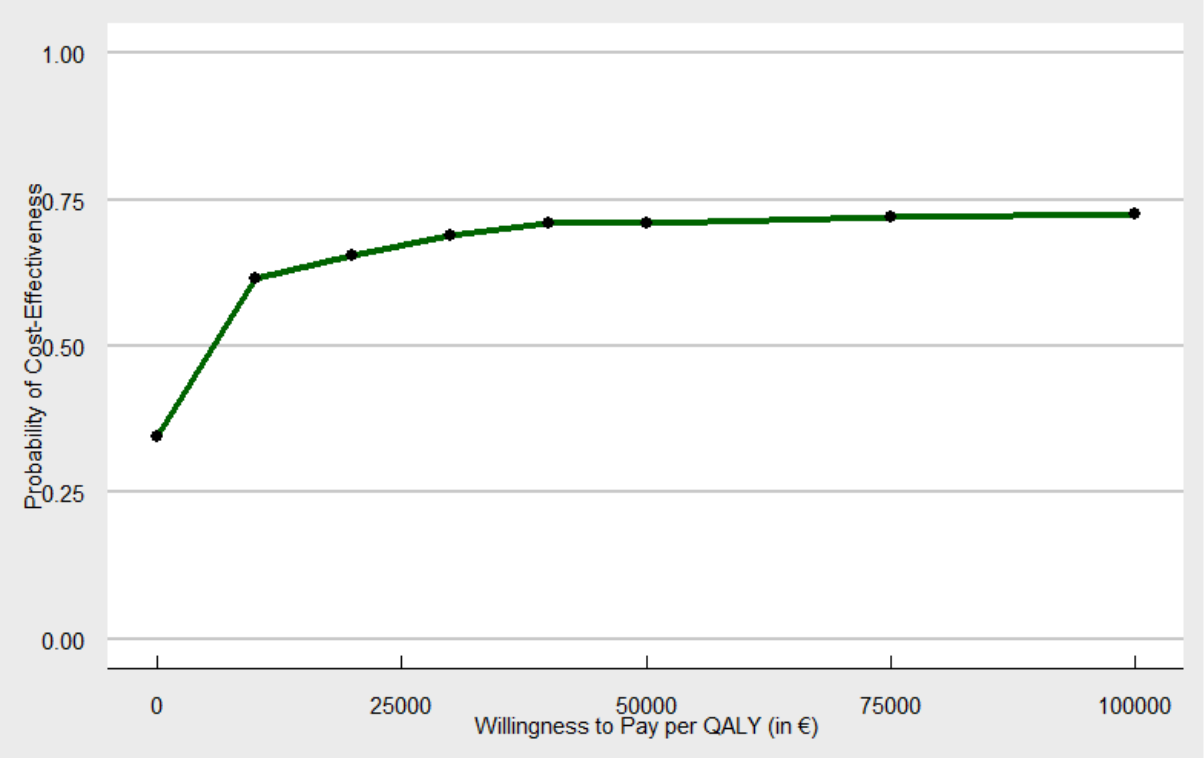



**Figure 11.** Cost-Effectiveness Acceptability Curve

# 6. Discussion

This master thesis was the first to study and analyze the potential cost-effectiveness of the Check@Home screening program in the general population of the Netherlands. A non-constrained DES model was developed to evaluate the health economic impact of usual care compared to Check@Home screening. This Chapter starts with a discussion of the main findings (Section 6.1). Subsequently, remarkable results are discussed in Section 6.2, including possible explanations. In Section 6.3, we briefly discuss our results in comparison with the literature. The possible impact of the structural assumptions in the health economic model on the results is discussed in Section 6.4. Next, in Section 6.5, the research limitations are discussed. Finally, recommendations for future research are provided in Section 6.6.

## 6.1. Main Findings

The base-case deterministic analysis showed that screening, compared to usual care, resulted in lower costs (i.e., - €25.13) and better health effects per patient (i.e., + 0.014 LYs and + 0.010 QALYs), leading to an ICUR of - €2,519.48. The ICUR implied that the Check@Home screening program was dominant and cost-saving compared to usual care. The incremental costs and effects on the individual level seemed marginal. However, when we put the results in the perspective of the total target population (i.e., 50-75-year-olds in the Netherlands), the screening strategy saved €142,327,781 and yielded 56,491 QALYS and 73,235 LYs, compared to the usual care strategy.

Secondary outcomes showed fewer CVD complications in the screening strategy than in the usual care strategy (i.e., from 2830 to 2816 CVD complications per 10,000 individuals). Furthermore, of the patients with CKD, fewer progressed to kidney failure (i.e., from 408 to 406 per 10,000 individuals). Of the patients who still progressed to kidney failure, fewer received RRT. The average time until a CVD complication and kidney failure progression were later in the screening strategy than in usual care. CVD complications and RRTs are very costly, with a significant impact on the patient's quality of life. Therefore, the reduction in CVD complications and RRTs appeared to be the reason why the costs per patient were lower, and the health effects per patient were better in the screening strategy compared to the usual care strategy.

Furthermore, at the end of the simulation, there were proportionally more patients diagnosed than undiagnosed in the screening strategy than in the usual care strategy, implying that the screening program effectively detected diseases. Moreover, at the end of the simulation, patients were generally in less advanced disease stages in the screening strategy than in the usual care strategy, implying that screening effectively delayed disease progression.

In addition to the base-case scenario, we evaluated an optimistic and pessimistic scenario for screening. In the optimistic scenario (i.e., higher participation rates, lower screening costs, and higher diagnostic performance than the base-case scenario), the ICUR was equal to -€98.34. The ICUR implied that screening in an optimistic scenario was dominant and cost-saving compared to usual care. In the optimistic scenario, the costs per patient and the health effects per patient were higher than in the base-case scenario. The higher costs per patient can be explained by the fact that screening in an optimistic scenario leads to more new diagnoses than in the base-case scenario. As more individuals are diagnosed, extra costs are made for treating those individuals earlier. Furthermore, in the optimistic scenario for screening, CVD complications and RRTs occur

later than in the base-case strategy. When CVD complications and RRTs occur later, patients experience a higher quality of life for longer, leading to higher average health effects in the optimistic scenario.

In a pessimistic scenario (i.e., lower participation rates, higher screening costs, and lower diagnostic performance than the base-case scenario), the ICUR was -€4,488.79. The ICUR implied that screening in a pessimistic scenario was still dominant and cost-saving compared to usual care. In the pessimistic scenario, the costs per patient were higher, and the health effects were lower compared to the base-case scenario for screening. In the pessimistic scenario, more CVD complications occurred, and more CKD patients progressed to kidney failure than in the base-case scenario. Among patients with kidney failure, more patients received RRT in the pessimistic scenario than in the base-case scenario. Since CVD complications and RRTs are expensive, this appears to be the reason why the costs per individual in the pessimistic scenario are higher than in the base-case scenario. Moreover, the costs per home-based test (Table 31) were higher in the pessimistic than in the optimistic scenario.

To evaluate how uncertain the health economic outcomes are due to parameter uncertainty, we performed a PSA. The mean results from the PSA showed that screening, compared to usual care, decreased the costs per patient by €1.68 and increased QALYs per patient by 0.010, resulting in a mean ICUR of - €173.86. The difference between the base-case deterministic analysis results and the PSA's mean results was relatively small. In both the deterministic analysis and the PSA, screening leads to lower costs per patient and higher health effects. However, it is still questionable whether the PSA results are stable, given the low number of runs and relatively low number of individuals simulated.

The incremental cost-effectiveness plane (Figure 10) showed that the outcomes of the incremental costs and incremental QALYs could be in all four quadrants, implying uncertainty around the outcomes of the health economic model. Changes in the model inputs significantly affect the cost-effectiveness outputs of the health economic model. This also affects whether screening is cost-effective or not. The cost-effectiveness acceptability curve (Figure 11) showed that at a WTP threshold of €20,000 per QALY, there is a 65.5% probability of screening being cost-effective. Additionally, Figure 11 showed that even at very high WTP thresholds, screening could never be 100% cost-effective.

## 6.2. Remarkable Results

Some remarkable results appeared in the deterministic analyses of this health economic evaluation. In this Section, we discuss these results and provide possible explanations. First, the number of CVD complications was higher in the optimistic scenario (i.e., 56,340 CVD complications) than the base-case scenario for screening (i.e., 56,321 CVD complications). The difference of 19 CVD complications seems marginal, yet remarkable. One would typically expect that, in an optimistic scenario (i.e., where more individuals are diagnosed and treated earlier compared to the base-case scenario), fewer CVD complications occur. A possible explanation is that the survival was higher in the optimistic scenario: the mean life years were 21.957 years in the base-case scenario and 21.978 years in the optimistic scenario for screening. As individuals get older in the optimistic scenario, there is more time for individuals to experience a CVD complication. The average time until individuals experienced a CVD complication also increased from 17.61 years in the base-case scenario to 17.67 years in the optimistic scenario. Another

possible explanation for why more CVD complications occurred in the optimistic scenario is that the distribution of the diseases present in the diseased population is different in the base-case and optimistic scenario (Appendix 10, Figure 13). For example, there were proportionally more patients with AF, CAD, and HF in the optimistic scenario (43.3%) compared to the base-case scenario (43.1%). Different diseases have different associated CVD risks.

Another remarkable result is that there were proportionally more kidney failure patients who received RRT in the pessimistic screening scenario (72.6%, 5921 RRTs out of 8161 kidney failure patients) than in the usual care strategy (72.1%, 5893 RRTs out of 8169 kidney failure patients). Although some model inputs in the pessimistic scenario were less favorable than the base-case scenario for screening, one would expect that screening still leads to fewer patients receiving RRT than in the usual care strategy. A possible explanation for this result is that, at the end of the health economic model, the proportion of individuals with CKD was higher in the pessimistic scenario (20.0%) than in the usual care strategy (19.9%) (Appendix 10, Figure 13). As more individuals had CKD in the pessimistic scenario, more individuals were at risk of progressing to kidney failure and thus receiving RRT.

## 6.3. Comparison with Literature

To our knowledge, the Check@Home screening program is the first home-based population-based screening program for the early detection and treatment of the combination of CVD (i.e., AF, CAD, and HF), CKD, and DM2 in the Netherlands and beyond. Appendix 4 presented a brief overview of previous health economic evaluations since 2016. The overview showed that population-based AF screening (i.e., with a handheld ECG recorder) was cost-saving in a Swedish study (Lyth et al., 2023) and cost-effective in a Belgian study (Proietti et al., 2019). Both studies showed that AF screening prevented CVD complications and was especially effective among the elderly population (i.e., over 75 years). Søgaard et al. (2022) studied the cost-effectiveness of population-based CVD screening among men aged 65-74 in Denmark. Their study showed that screening men for CVD at a WTP threshold of €20,000 was cost-effective at a 73% probability. Jürlicher and Varounis (2022) studied the cost-effectiveness of CVD screening in a high-risk (Kazakhstan) and low-risk country (Germany) in a population aged 40-65 years. Their research showed that CVD screening prevented CVD complications and was cost-saving in Kazakhstan and cost-effective in Germany. Finally, preliminary results from the THOMAS study showed that home-based population screening to detect unknown CKD was cost-effective with an ICER of €9,204. When we compare the literature with the results from this master thesis, there is some overlap. Our research showed that the Check@Home screening program is cost-saving in the base-case analysis and yields better patient outcomes. Similar to the literature, our health economic model also showed cost-effective results. However, the probabilistic sensitivity analysis of our model showed that there is uncertainty in the health economic outcomes. Furthermore, it is important to emphasize that the previous health economic evaluations have not evaluated combination screening for CVD, CKD, and DM2.

## 6.4. Structural Assumptions

We made several structural assumptions in the health economic model. These assumptions could have had unintended adverse effects on the results. In this section, we discuss these assumptions and their possible impact on the cost-effectiveness of screening.

First, when an undiagnosed individual visited the GP, we assumed that the GP always found the right disease. Therefore, patients always enter the right diagnostic and treatment pathway. In reality, the GP may not detect the disease, or the GP may suspect the wrong disease. As a result, patients could end up in the "wrong" diagnostic and treatment pathway, leading to extra diagnostic procedures and possibly the wrong treatment. Extra diagnostic procedures result in additional costs. The wrong treatment could result in ineffective treatment, and so an increased risk of experiencing complications and progression. On the other hand, one could argue that there is some overlap between the five diseases regarding diagnostic procedures and treatment. Therefore, one could assume that after a series of similar diagnostic procedures, the GP or medical specialist has already detected the right disease. Furthermore, the "wrong" treatment could still be effective since many diseases are treated similarly.

Furthermore, we assumed that all diagnosed patients comply with the treatment provided by the GP and medical specialist. Compliance directly impacts the actual effectiveness of a treatment in the real world. A model that ignores compliance might overestimate the effectiveness of the treatment and underestimate the risk of complications and progression. Therefore, ignoring compliance could result in overestimating the cost-effectiveness of screening.

Another assumption in the health economic model is that no comorbidity was considered. In reality, we know this is not the case. For example, DM2 is a known risk factor for developing cardiovascular diseases (Hartstichting, n.d.-c). However, including comorbidity in the model would have been very complex since we have five disease domains to consider. If we included comorbidity, we would need to know the increased risk of developing a new disease, progressing to a more advanced stage, complications, and the effectiveness of treatment for all combinations of diseases. Since we did not have individual patient data, many assumptions would have to be made. Therefore, in this health economic model, it was decided to exclude comorbidity. Excluding comorbidity is a conservative assumption, resulting in underestimating the actual risk of progression and complications, such as CVD complications.

Moreover, progression was assumed to be unidirectional. Therefore, patients were unable to regress to a less severe stage. In reality, with the right treatment, complaints could be reduced, and, in some cases, patients regress to a less severe disease stage. For example, HF patients could regress to a lower NYHA class (van Giessen et al., 2016), and CKD patients could regress to a lower CKD stage (Boersma et al., 2010). Patients who regress to a less severe stage have a reduced risk of complications. Therefore, assuming patients can only progress to a more advanced stage is a conservative assumption, resulting in overestimating the actual risk of complications.

We also assumed that individuals could only experience one CVD complication in the model. In reality, if an individual survived a CVD complication, the individual could experience a second event (or more), resulting in extra costs and a reduction in quality of life. Therefore, assuming individuals could only experience one event could lead to lower costs, higher quality of life, and higher survival.

Furthermore, we assumed that CKD patients who experienced a CVD complication could not progress to kidney failure. Hence, they could not receive RRT. Additionally, CKD patients who progressed to kidney failure (and thus received RRT or conservative treatment) could not experience a CVD complication. In reality, both events could happen. Therefore, this assumption leads to lower costs and a higher quality of life than reality. Therefore, this assumption could result in overestimating the cost-effectiveness of screening.

Finally, we made several assumptions about the undiagnosed population. These assumptions focused on the size of the undiagnosed population, the stage distribution among the undiagnosed population, and the probability of getting diagnosed. The group size was estimated based on an approximation from the Check@Home consortium. However, if the undiagnosed population is larger than estimated, one would expect to diagnose more individuals through screening. In contrast, fewer individuals would be diagnosed through screening when the undiagnosed population is smaller than estimated. Furthermore, for the disease domains AF, HF, and CKD, we assumed that the stage distribution among the undiagnosed population was 66.7% in the first disease stage and 33.3% in the second. Therefore, this assumption could significantly impact the risk that undiagnosed individuals are exposed to. Individuals in more advanced disease stages have higher risks of complications. Another assumption we made about the undiagnosed population is the probability of getting diagnosed at a specific disease stage. We classified all disease stages into low, middle, high, and very high stages. Subsequently, we assumed that the probability of getting diagnosed was 10%, 50%, 85%, and 100%, respectively. These probabilities greatly influence when and at which disease stage individuals are diagnosed. In Chapter 3, we evaluated the impact of the last two assumptions on the outcomes of the health economic model. The evaluation showed that the assumptions have a significant impact on the ICUR and whether screening is cost-effective or not. This highlights the necessity of making the right choices in a future health economic model for Check@Home (see future research, Section 6.6).

## 6.5. Research Limitations

This section presents the research limitations of this master thesis. First, this health economic evaluation was reflected from a healthcare perspective. Therefore, we only considered the costs and effects of the Dutch healthcare system. However, guidelines from the National Healthcare Institute of the Netherlands also recommend considering the costs and effects associated with productivity loss (e.g., individuals who do not recover after an ischemic stroke can no longer work), patient- and family-related costs, and cost and effects in other sectors (ZiN, 2016).

Furthermore, to populate the model, we used input from publicly available sources, such as the Dutch National Statistics, Nivel Care Registry, and evidence from cohort studies. If we had individual patient data available, we could better represent the Dutch general population aged 50-75.

This health economic evaluation focused on the five disease domains: AF, CAD, HF, CKD, and DM2. The diseases are complex regarding disease development, disease stages, progression, comorbidity, complications, treatment, quality of life, Etc. During this master thesis, we only had limited time available. Therefore, we had to make several assumptions to simplify the diseases. More time is needed to understand the complexity within and between the five disease domains to model the diseases appropriately.

Furthermore, the Event Specific Distribution (ESD) approach was applied to determine which event occurs at the corresponding event time. According to Degeling et al. (2019), other approaches outperform the ESD approach. However, these other approaches require individual patient data. Limitations of the ESD approach are that a high number of competing events ensures that events generally occur earlier in the simulation model. Furthermore, the relative number of occurring events may not correspond to reality. For example, events that occur relatively infrequently or with a right-skewed time-to-event distribution may occur less frequently in the

model than in reality. Due to time constraints, we could not validate the results and relative incidence of the events with (healthcare) professionals.

Another limitation is that the 10-year CVD risks calculated with the SCORE2 and SMART2 prediction models were assumed to be constant over 10-year periods. Therefore, age only affected CVD risk per 10-year period. However, we know age is a significant contributor to CVD risk. An implication of assuming that the CVD risk is constant over 10-year periods is the overestimation of the true risk in the first years and the underestimation of the true risk in the last years.

In addition to the limitations in the health economic model, this master thesis also had limitations in the analyses that were performed. In the deterministic analysis, the health economic impact was only evaluated for usual care compared to screening in a base-case, optimistic, and pessimistic scenario. In the optimistic and pessimistic scenario, we simultaneously changed a selection of model inputs. In addition, it would have been relevant to perform a one-way deterministic sensitivity analysis by adjusting one screening input at a time, allowing us to observe better the effect of each screening input on the health economic impact of screening.

Furthermore, we only performed 200 runs for 50,000 individuals in the PSA. Usually, 1,000 runs are considered a minimum. It is better to evaluate the PSA for 5,000 or 10,000 runs. Performing a PSA with only 200 runs can lead to limited exploration of uncertainty. Therefore, 200 runs may not sufficiently capture the full range and distribution of parameters, potentially resulting in less reliable estimates of cost-effectiveness and the associated uncertainty. This could lead to incomplete insights into the robustness of the economic evaluation results. Furthermore, evaluating a minimum of 100,000 individuals per PSA run rather than 50,000 would have been better. Now, the uncertainty in the PSA could be partly caused by the instability of the results rather than parameter uncertainty. We had no high-performance computer available, and due to time restrictions, we decided to evaluate the PSA for 200 runs with 50,000 individuals.

Finally, due to time limitations, no validations were performed on the assumptions, model inputs, and results with clinical experts. Validating the assumptions and results would improve the quality and credibility of this research. Clinical experts can help identify potential shortfalls in the model and reduce uncertainty in the assumptions made. Furthermore, clinical experts must be able to understand and interpret the results.

## 6.6. Future Research

We identified valuable future research based on the main findings and the research limitations. The topics are divided into (1) extending the model, (2) extending the simulation and analyses, and (3) other.

*Extending the Model*

We have several recommendations for extending the health economic model. First, the current health economic model focuses on a one-off screening strategy. For a future model, we recommend also evaluating the health economic impact in case of repetitive screening, for example, by inviting individuals every two or five years.

Furthermore, we recommend representing the undiagnosed population more accurately. In the current health economic model, several assumptions were made about the size of the

undiagnosed population, the stage distribution among this population, and the probability of getting diagnosed at different disease stages. More time and effort is needed to make good assumptions about the undiagnosed population. For example, this can be done by verifying the assumptions with clinical experts or retaining empirical studies focused on the undiagnosed population. Relevant data are incidence and prevalence among the undiagnosed population, progression among the undiagnosed population, and stage distribution at diagnosis.

In a future health economic model, we also recommend including the possibility of a second CVD complication (or more). The SMART2 risk prediction model might be an appropriate tool since it can be used in patients with previously identified CVD.

Another recommendation for extending the health economic model is to allow patients to develop multiple diseases (i.e., include comorbidity). To realize this, it is essential to understand the complexity and the relationship between the five disease domains. This would allow us to better model the diseases, including the increased risk of developing other diseases, complications, and the effectiveness of treatment. For this, we recommend collaborating with clinical experts in other work packages in the Check@Home consortium and using future available individual patient data.

Furthermore, we recommend incorporating adherence and treatment compliance in a future health economic model. A model that ignores adherence and compliance might overestimate the effectiveness of the treatment. Accounting for adherence and compliance in a future health economic model allows a more accurate estimation of treatment outcomes. Therefore, we advise gathering data on adherence and compliance from existing studies, clinical trials, patient records, or other sources. This data may include medication adherence rates, treatment completion rates, and control visit attendance.

In a future health economic model, we recommend studying other disease-related complications (e.g., diabetic foot and diabetic retinopathy). To do this, we recommend evaluating the range of complications that might occur in CVD, CKD, and DM2 patients. Furthermore, data needs to be gathered about the number of people suffering from those complications and whether the costs and effects associated with the complications are significant enough to include in a future health economic model.

*Extending the Simulation and Analyses*

In addition to recommendations for extending the model, we also recommend to extend the analyses and simulations. First, we advise performing a one-way deterministic sensitivity analysis. It would be relevant to do such analyses for the selected model inputs in the optimistic and pessimistic scenarios and other model inputs. For those model inputs with a significant effect on the health economic outcomes, it is worthwhile to see whether we have control over the input and whether we can collect more information about it.

Our second recommendation is to extend the PSA by increasing the number of runs to at least 1000 and the number of individuals per run to 100,000. Currently, the uncertainty in the PSA outcomes could be partly due to the instability in the results rather than parameter uncertainty.

Another recommendation for future analyses is to perform the deterministic analysis (and possibly the PSA) without discounting the costs and effects. These results would provide insights into the effect of discounting on the cost-effectiveness of screening. The benefit of screening may be greater, but the discount rates reduce the effects.

Furthermore, the diverse outcomes in the incremental cost-effectiveness plane highlight the necessity of addressing and understanding parameter uncertainty. We recommend performing a value of information analysis (VOI). The expected value of partially perfect information (EVPPI) would be especially interesting to assess. The EVPPI measures the value of reducing uncertainty in specific model parameters. The EVPPI helps understand the value of obtaining more precise information about uncertain parameters within a health economic model (Rothery et al., 2020). EVPPI is particularly valuable in identifying which parameters contribute the most to uncertainty in model outcomes and related decision uncertainty. A simple method to measure the EVPPI is to store the model inputs and outputs per PSA run and use the SAVI-tool (Strong et al., 2014).

Furthermore, it would be interesting to know how the mean costs per patient are broken down. For example, how much of the costs contribute to the screening program, how much contributes to treating patients, and how much contributes to CVD complications and RRTs? In future analyses, knowing where the costs come from can be helpful, as it gives insights into how changes in model inputs affect the health economic outcomes.

Finally, we recommend evaluating more intermediate outcomes, such as the stage at diagnosis. Furthermore, it would be interesting to evaluate the intermediate outcomes (i.e., secondary outcomes) at different points in time in the health economic model. Not only at the end of the simulation, when everyone died, but also after ten years for example.

*Other*

Other recommendations for future research are performing the health economic evaluation using a societal perspective. For this, more data needs to be collected. For example, data is needed about the costs and effects of productivity loss (e.g., how many people are no longer able to work after experiencing a CVD complication or starting RRT? What are the societal costs?), patient- and family-related costs (e.g., transportation costs to go to the regional diagnostic center for extensive screening), and costs and effects in other sectors. Finally, we recommend validating the assumptions, model inputs, and results with clinical experts and modeling experts to improve the quality of the model and the credibility of the results.

# 7. Conclusion

The objective of this master thesis was to evaluate the potential health economic impact of the Check@Home screening program on the general population of the Netherlands aged 50-75 years. Furthermore, we aimed to develop the first health economic model for the HTSR group to lay the foundation for future model development and decisions on potential valuable future research. The objective led to the main research question: "*What is the expected health economic impact of a national home-based screening program for the early detection and treatment of CVD, CKD, and DM2, compared to usual care in the Netherlands?*".

A non-constrained discrete-event simulation model was developed to evaluate the health economic impact of usual care compared to the Check@Home screening program over a lifetime horizon. The base-case deterministic analysis results support the potential cost-effectiveness of screening and improved patient outcomes. On the individual level, screening saved €10.32 per patient, yielding 0.006 QALYs and 0.012 LYs per patient. In the total target population, screening potentially saved €142,327,781 and yielded 56,491 QALYs and 73,235 LYs compared to usual care.

The PSA emphasized uncertainty around the outcomes in the health economic model. Results from the incremental cost-effectiveness plane showed that the incremental costs and effects could be in all four quadrants, implying that changes in model inputs result in uncertainty in the cost-effectiveness of screening. Furthermore, the cost-effectiveness acceptability curve showed that at a WTP of €20,000, there is a 65.5% probability of screening being cost-effective.

Overall, this master thesis suggests that a national home-based screening program for CVD, CKD, and DM2 in the general population of the Netherlands holds promise. Screening, compared to usual care, could potentially be cost-effective and improve patient outcomes. However, due to uncertainty in the outcomes of the health economic model, the question remains how certain we are about the cost-effectiveness of screening. Therefore, a future health economic model should focus on removing uncertainty in model inputs and outcomes.

# Appendix

## Appendix 1: Disease Domains

The Check@Home study distinguishes between five disease domains, consisting of atrial fibrillation (AF), coronary artery disease (CAD), heart failure (HF), chronic kidney disease (CKD), and type 2 diabetes (DM2) (Check@Home, 2022). The five disease domains are interrelated and share common risk factors. This appendix provides a general description of the five disease domains. Table 38 gives an overview of the symptoms, risk factors, complications, diagnostic options, and treatment options.

*Atrial Fibrillation*

Atrial fibrillation (AF) is a heart rhythm disorder. The contraction of the atrium (front chamber of the heart) is uncoordinated, and usually faster than normal (NHG, 2017). Signs and symptoms of AF are an irregular heartbeat, chest discomfort or pain, shortness of breath, being light-headedness, or fatigue. Risk factors for AF are an advanced age, smoking, hypertension, obesity, diabetes, and a sedentary lifestyle (NHG, 2017). According to Stewart et al. (2001), AF is associated with an increased risk of forming blood clots. These clots can travel to the heart or brain, and block blood vessels, leading to a myocardial infarction or a stroke. Other complications of AF are heart failure, fatigue, and reduced quality of life (Stewart et al., 2001). When AF is diagnosed, it is classified into paroxysmal, persistent, and permanent AF. To treat AF, patients typically receive lifestyle advice (e.g., avoiding coffee, alcohol, drugs, and heavy meals) and medication. Medication often consists of drugs to control the heart rhythm (e.g., beta-blockers and calcium channel blockers) and a antithrombotic (medication to prevent blood clots: also called anticoagulants or blood thinners). Patients diagnosed with persistent AF are eligible for cardioversion or ablation surgery. Cardioversion help restore a normal heart rhythm by using electric shocks or medication. Ablation surgery is a treatment for abnormal heart rhythms by blocking electrical pathways in the heart (NHG, 2017).

*Coronary Artery Diseases*

Coronary artery disease (CAD), also called ischemic heart disease, is a condition that occurs when the coronary arteries, the blood vessels that supply the heart muscle with oxygen and nutrients, become narrowed or completely blocked. This narrowing or blockage is caused by the build-up of plaque (i.e., atherosclerosis), a substance of cholesterol and fat that can accumulate in walls of the arteries. Over time, the narrowed or blocked blood vessels reduce the blood flow to the heart muscle (Malakar et al., 2019). CAD is a complex disease and is manifested by stable angina pectoris, unstable angina pectoris, myocardial infarction, or sudden cardiac arrest (Malakar et al., 2019). According to Pizzi et al. (2016), CAD can also be classified into obstructive and non-obstructive CAD. Non-obstructive CAD is usually defined as < 50% plaque in the coronary arteries. Whereas obstructive CAD is defined as ≥ 50% plaque in the coronary arteries. Signs and symptoms of CAD are chest discomfort or pain, shortness of breath, pain in the left shoulder or arm, sweating, and nausea. However, sometimes CAD occurs without obvious signs or symptoms. Risk factors for developing CAD are hypertension, high cholesterol level, smoking, obesity, diabetes, lack of physical activity, family history of heart disease, and high-stress level (NHG, 2019b, 2022). CAD can lead to a myocardial infarction which can cause damage to the heart muscle. Because of this damage, patients can develop heart failure and heart rhythm disorders (Malakar et al., 2019). When CAD is diagnosed, treatment typically involves a combination of lifestyle changes and medication. Lifestyle changes include quitting smoking, healthier diet,

exercising regularly, and maintaining a healthy weight. Patients diagnosed with stable angina pectoris get medication to control the heart rhythm such as beta-blockers or calcium antagonists. Additionally, patients can get treatment for hypertension (e.g., ACE-inhibitors) or cholesterol-lowering drugs (e.g., statin). Patients diagnosed with unstable angina pectoris get similar treatment. Usually, antithrombotics are added. Other treatment options include angioplasty treatment (i.e., widening the narrowed artery) or bypass surgery (i.e., rerouting blood flow) (Hartstichting, n.d.-b; NHG, 2019a, 2019b, 2022).

*Heart Failure*

In heart failure (HF), the pumping function of the heart is not working properly. As a result, too little blood is circulated around the human body. HF is often caused by a damaged heart muscle or because the heart gets too little blood. A damaged heart muscle can be caused by a prior myocardial infarction, hypertension, or heart rhythm disorders (Hartstichting, 2022). The most common signs and symptoms of people with HF are fatigue, shortness of breath, cold feet and hands (due to poor blood circulation), and the retention of moisture around the lungs, abdomen, legs, and ankles (Hartstichting, 2022). Risk factors of HF are a history of heart disease, hypertension, smoking, alcohol or drug use, eating and lifestyle habits such as salty and fatty foods, and little exercise (Hartstichting, 2022). If left untreated, HF can cause a sudden cardiac arrest, or it causes blood clots to travel to the lungs, aorta, or brain. When HF is diagnosed, it is generally classified into HFpEF, HFmrEF, and HFrEF. A cardiologist typically treats HF based on the severity of the patient's symptoms. The severity of symptoms can be measured through the classification of the New York Heart Association (NYHA), ranging from NYHA-I (no complaints) to NYHA-IV (severe complaints, also at rest) (NHG, 2021). Treatment mainly consists of lifestyle advice, medication to control blood pressure (i.e., ACE-inhibitors), diuretics, and SGLT-2 inhibitors (NHG, 2021).

*Chronic Kidney Disease*

Kidneys that work properly remove waste, toxins, and excess fluid from the human body. They also help to control blood pressure. Chronic kidney disease (CKD) is a progressive condition in which the kidney is damaged and cannot filter blood as well as it should (CDC, 2022). Usually, CKD is caused by kidney inflammation, diabetes, or high blood pressure. Patients with CKD do not always notice any signs or symptoms at an early stage. However, as the condition worsens, symptoms can occur. Possible symptoms of CKD are anemia, hypertension, skin complaints, itch, nausea, fatigue, and other complaints (Nierstichting, n.d.-b). CKD risk factors are diabetes, hypertension, heart disease, family history of CKD, and obesity (CDC, 2022). If left untreated, CKD can progress to kidney failure and CVD. To diagnose CKD, the estimated glomerular filtration rate (eGFR) and the albumin-creatine ratio (ACR) are measured. Based on the eGFR and ACR, CKD is classified into mild, moderate, or severe CKD. If the eGFR and ACR deteriorate even further, it can lead to kidney failure. According to NHG guidelines, treatment of CKD typically focuses on managing the underlying causes of the condition and slowing its progression. Depending on the stage and severity of CKD, several treatment options are available. Treatment of CKD mainly consists of a healthier lifestyle (e.g., eating less salty food), medication to control blood pressure (e.g., ACE-inhibitors), and SGLT-2 inhibitors. When CKD progresses to kidney failure, patients can receive renal replacement therapies, such as dialysis or kidney transplantation (NHG, 2018).

*Type 2 Diabetes*

Type 2 diabetes (DM2) is a chronic condition that affects how the body processes glucose. The symptoms of DM2 can be mild and may not be noticeable at first. They can include increased thirst and urination, fatigue, blurred vision, slow-healing wounds or infections, and weight loss or gain (Diabetes Fonds, n.d.-c). Risk factors for DM2 include little exercise, obesity, eating unhealthy, smoking, advanced age, and family history of diabetes. Certain ethnic groups also have an

increased risk of DM2 (Diabetes Fonds, n.d.-c; Volksgezondheid en Zorg, n.d.). If left untreated, DM2 can lead to CVDs such as a myocardial infarction or a stroke. DM2 can also cause complications, such as blindness, kidney disease, diabetic foot, and various types of cancer (Volksgezondheid en Zorg, n.d.). According to NHG guidelines, to diagnose DM2 blood tests are performed to measure the blood sugar. With a blood sugar level between 6.1 mmol/L and 7.0 mmol/L, individuals are diagnosed with prediabetes (impaired glucose tolerance). With a blood sugar level higher than 7.0 mmol/L, the patient is diagnosed with DM2. Treatment for DM2 typically involves lifestyle advice, such as a healthy diet, regular exercise, and weight management, as well as medications to lower blood sugar levels and manage other health conditions that may be present. DM2 patients at risk of CVD get ACE-inhibitors or SGLT2-inhibitors. In some cases, insulin therapy may be necessary to help control blood sugar levels (NHG, 2023).

**Table 38.** Description, symptoms, risk factors, causes, and diagnostic and treatment options of the five disease domains.

| Disease | Description | Symptoms / signs | Risk factors | Complications | Diagnostic options | Treatment options |
|---|---|---|---|---|---|---|
| **AF** | Heart rhythm disorder, where the contraction of the atrium is uncoordinated and faster than usual | Irregular and fast heart beat; chest discomfort or pain; shortness of breath; light-headed; fatigued | Advanced age; smoking; too much alcohol; hypertension; obesity; diabetes; sitting lifestyle | Forming of blood clots leading to myocardial infarction (MI) or stroke (IS and ICH); heart failure; fatigue | Anamnesis; basic examinations; ECG; event recorder; Holter examination. | Lifestyle advice; medication to control heart rhythm; antithrombotic (i.e., anticoagulants); cardioversion; ablation |
| **CAD** | Narrowed or blocked coronary arteries (due to plaque) that reduce the blood flow and oxygen to the heart muscle | Chest discomfort or pain; shortness of breath; pain in left shoulder or arm; sweating; nausea | Hypertension; high cholesterol level; smoking; obesity ; diabetes; lack of physical activity; family history of heart disease; high stress level | Myocardial infarction (MI); (un)stable angina pectoris; damage to the heart muscle; heart failure (HF); heart rhythm disorders | Anamnesis; basic examinations; ECG (rest or exercise); laboratory tests; echocardiogram; coronary angiography; CT-scan; MRI-scan; MPS. | Lifestyle advice; medication to control heart rhythm; medication to control blood pressure; cholesterol-lowering drug; antithrombotic; bypass surgery; angioplasty treatment |
| **HF** | Pumping function of the heart is not working properly, because the heart is damaged or gets too little blood | Fatigue; shortness of breath; cold feet and hands; retention of moisture around the lungs, abdomen, legs, and ankles | Hypertension; smoking; alcohol or drug use; too salty or fatty food; little exercise; history of heart disease | Cardiac arrest; myocardial infarction (MI); angina pectoris; stroke (IS and ICH) | Anamnesis; basic examinations; blood tests (to measure (NT-pro)BNP); ECG; echocardiogram | Lifestyle advice; medication to control blood pressure; diuretics; SGLT2-inhibitors |
| **CKD** | Damaged kidney that cannot filter the blood as good as it should | Anemia; hypertension, skin complaints; itch; nausea; fatigue | Diabetes; hypertension; heart diseases; family history of CKD; and obesity | Kidney failure; increased risk of CVD (stroke or myocardial infarction). | Anamnesis; basic examinations; Laboratory test (to measure eGFR and ACR); CT-scan; MRI-scan; ultrasound; kidney biopsy. | Lifestyle advice; medication to control blood pressure; SGLT-inhibitors; renal replacement therapy |
| **DM2** | Chronic condition where the body becomes resistant to the hormone insulin that leads to high blood sugar level and other health problems | Thirsty; increased urination; fatigue; blurred vision; slow-healing wounds or infections; weight loss or gain | Little exercise; obesity; eating unhealthy; smoking; advanced age; family history of diabetes | Increased risk of CVD (myocardial infarction or stroke); blindness; kidney disease; diabetic foot; cancer | Laboratory test (to measure blood sugar and risk factors) | Lifestyle advice; medication to control blood sugar level; insulin therapy; medication to control blood pressure |

## Appendix 2: Key Concepts in Health Economic Evaluations

An economic evaluation is "the comparative analysis of alternative courses of action in terms of both their costs and consequences." (Drummond et al., 2015). In health economic evaluations, the comparison is usually between alternative healthcare interventions, policies, or programs. These evaluations aim to provide decision-makers, such as policymakers, healthcare providers, and payers, with systematic evidence-based information to inform resource allocation and policy decisions in the healthcare sector. Research in health economic evaluation is often concerned with the question of whether a particular healthcare intervention is valuable compared to other interventions, that could be paid for with the same budget (Drummond et al., 2015).

Different methods for health economic evaluations exist, including cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost-utility analysis (CUA). These methods all focus on the comparison of two or more alternatives. The main difference between the methods are the way health effects are measured and valued (Drummond et al., 2015). In a CMA the assumption is made that there is no difference in health effects between the options that are compared. If this assumption holds, the CMA is useful in identifying the cheapest option. However, the assumption that there is no difference in health effects is hardly ever valid. Therefore, the CMA is usually not a good analytical technique to choose (Drummond et al., 2015). In a CEA, the measure of effect can be any health outcome. For example, the number of weight loss after an obesity prevention program. The advantage of the CEA is that the measure of effect is an outcome that may be relevant to the audience of the analysis. However, comparing the results obtained from different health economic evaluations is not always possible, because different measures of effects are used (Drummond et al., 2015). In a CBA, all effects of interest (i.e., both cost and health effects) are translated into monetary units. As a result, different healthcare interventions, across different conditions, can easily be compared. The question remains how to translate health effects into money (Drummond et al., 2015). The CUA uses the Quality Adjusted Life Years (QALYs) as the standard measure of effect. This standard measure of health effect can be used across multiple health economic evaluations. A QALY is calculated by combining "length of life" with "quality of life" (Drummond et al., 2015). Different types of instruments can be used to measure health-related quality of life. In health economic evaluations, one often measures quality of life through generic instruments. Guidelines from the National Healthcare Institute of the Netherlands recommend the EQ-5D-5L (ZiN, 2016). Subsequently, the measured quality of life is converted into a utility value between minus infinity and 1 (perfect health). A utility value of 0 represents death. A utility value lower than 0 represents a quality of life worse than death. According to Dutch guidelines, a CUA should be performed as standard (ZiN, 2016). In addition to an economic evaluation, a Budget Impact Analysis (BIA) can be performed. A BIA provides information about the financial consequences and affordability of the intervention. A CEA may indicate that a new healthcare intervention has good value relative to the current standard of care. A BIA may show that the new intervention is not affordable, and therefore not feasible (ZiN, 2016).

Once the total costs and health effects of two or more alternatives have been determined, they should be compared incrementally. The result of a CUA is called an incremental cost-utility ratio (ICUR) and is calculated by dividing the incremental cost of the new intervention by the incremental change in utility (Rudmik & Drummond, 2013). In practice, the terms ICUR and ICER are used interchangeably. When comparing two interventions, to get the best value for society's money, policy, and decision-makers want to implement interventions with the lowest ICER under the willingness-to-pay threshold (WTP) while taking into account several other factors. According to Rudmik and Drummond (2013), situations when policy and decision makers can

accept an intervention without the lowest ICER, include: 1) lack of an adequate alternative, 2) seriousness of condition (e.g., favor life-threatening conditions), 3) affordability from the patients perspective, and 4) predefined ethical objectives.

To present cost-effectiveness outcomes, a common method is the incremental cost-effectiveness plane (Rudmik & Drummond, 2013). On the x-axis, the incremental effects (i.e., QALYs for CUA) are displayed, while the y-axis displays the incremental costs of the new healthcare technology compared to usual care (i.e., current care). The incremental cost-effectiveness plane contains four quadrants, which may be used as an indication of the cost-effectiveness of the new healthcare technology (Drummond et al., 2015, p. 55). Two of the quadrants provide a simple answer to the cost-effectiveness of the new healthcare technology. When the result falls within the lower right quadrant, the new healthcare technology is dominant compared to usual care, meaning that it provides better health outcomes and is cheaper. In this case, the advice is always to accept the new healthcare technology. On the other hand, when the result falls in the upper left quadrant, the new healthcare technology is dominated by usual care. In other words, the new healthcare technology provides both worse health outcomes and it is more expensive. In this case, the advice is always not to accept the new healthcare technology. When the ICER falls in the upper right quadrant, the new healthcare technology provides better health outcomes, but it is more expensive than usual care. Moreover, when the result falls in the lower left quadrant, it means that the new healthcare technology provides fewer health benefits than usual care, but it is cheaper. In these two cases, the ICER is compared to the willingness to pay (WTP) threshold, which is the value that society is willing to pay for an additional unit of effects (or additional QALY). When the ICER falls above the WTP, the advice is not to accept the new healthcare technology. But, when the ICER falls below the WTP, the advice is to accept the new healthcare technology.

To determine the cost-effectiveness of a new healthcare intervention, CUA is used as a standard (ZiN, 2016). Other than the CUA, it is also relevant to look at intermediate outcomes to compare healthcare interventions. For example, in the Check@Home study insightful outcomes are the number of CVD complications and RRTs, and the time at which the CVD complications and RRTs occurs. This helps to understand the number of CVD complications and RRTs you can prevent. Other insightful outcomes for Check@Home are the number of new diagnoses through screening.

## Appendix 3: Health Economic Models

Models are a way of representing the complexity of the real world in a more simple and comprehensible form. Where true experiments, such as clinical trials, are sometimes infeasible or impractical, models can be used to simulate experiments and to explore alternative scenarios (Buxton et al., 1997). In the context of health economic evaluation, models are typically used in two situations. First, when no clinical trial has been conducted. And second, when a clinical trial only measures intermediate endpoints or has a short-term follow-up period. In the second case, (statistical) models can be used to extrapolate beyond the trial to final endpoints such as survival (Buxton et al., 1997). According to Caro et al. (2012), the range of modelling techniques for health economic evaluation has advanced substantially over the past decades. Popular modelling techniques in health economic evaluation are cohort state-transition models (e.g., Markov models), individual state-transition models (e.g., microsimulation models and first-order Monte Carlo), and discrete event simulation (Caro et al., 2012; Ethgen & Standaert, 2012).

*State-Transition Models*

According to Siebert et al. (2012) many clinical situations can be described in terms of the condition the patient is in ("states"), how the patient can move between such states ("transition"), and how likely such moves are ("transition probabilities"). State-transition models are models that work well in such clinical situations. Two common frameworks in healthcare are the cohort-based and the individual-level state transition model (Siebert et al., 2012). A cohort state-transition model simulates the transition of a hypothetical homogeneous cohort among various health states over time (Alarid-Escudero et al., 2023). A cohort state-transition model consists of a set of mutually exclusive and collectively exhaustive health states. The cohort is assumed to be homogeneous within each health state, meaning that the individuals in the cohort have the same characteristics and are indistinguishable from one another. The cohort can transition between health states with predefined probabilities. The transition probability represents the chance that individuals in a cohort can transition to another state or remain in the same state during a given cycle time. A common assumption made in cohort-based state-transition models is the "Markov" property, where it is assumed that the transition probabilities only depend on the current health state at any given cycle and cannot depend on the history prior to that cycle. This is an inherent limitation of cohort models (Siebert et al., 2012). According to Caro et al. (2012), the relative simplicity of cohort-based models still attracts many modelers and decision makers. However, there are situation when the decision problem demands taking the patient's history into account and individual-level models are required.

In contrast, individual-level state-transition models are not limited to the Markov property as they simulate one individual at a time (Siebert et al., 2012). Whereas cohort models are analysed as single cohorts progressing through the states simultaneously, individual-level models keep track of individual's history. A disadvantage of the individual model over the cohort-based model is that they are computationally intensive and often require high number of individuals to run through the simulation to obtain stable values (Siebert et al., 2012).

*Discrete-Event Simulation*

Another commonly used health economic model is a Discrete-Event Simulation (DES) model. The discrete handling of time in a DES model refers to the fact that DES moves forward in time at discrete time intervals, and that the events are discrete (i.e., mutually exclusive) (Karnon et al., 2012). DES is especially a good choice when patients are subject to multiple or competing risks. In this case, one can use patient data to describe specific event times rather than in cycle times. This can also be done in an individual-level state-transition model by making very short cycle

times. However, this would be very inefficient, since the model has to check whether an event has happened during every model cycle (Karnon et al., 2012). Other situations where DES is a good choice is when many patient characteristics are considered, especially when they change over time; when events depend on what happened before; when the effects of decisions made along the way are more of interest rather than only at the start (e.g., treatment decisions); and whenever healthcare or disease processes involve a series of associated events (Karnon et al., 2012).

## Appendix 4: Overview of Previous Health Economic Evaluations

The purpose of this Appendix was to gain insight into previous health economic evaluations of population screening on CVD, CKD, and DM2. A search was performed using the search engines Scopus and PubMed. The search aimed to find health economic evaluations of population-based or national-based screening in the five disease domains. We searched for articles between 2016 and 2023 (September). The following search string was used:

*("health economic evaluation" OR "cost-effective") AND ("population screening" OR "national screening" OR "home-based screening") AND ("cardiovascular disease" OR "atrial fibrillation" OR "coronary artery disease" OR "coronary heart disease" OR "heart failure" OR "chronic kidney disease" OR "type 2 diabetes")*

We deliberately choose not to include "Methods" in the search string, such as model types, to widen the scope a bit. The selection procedure is shown in figure 12. After removing duplicates, 22 articles were identified for screening. Subsequently, we excluded eight articles based on the title. Exclusion criteria were: non-English, not focused on western Europe or North America, or not primarily focused on CVD, CKD, or DM2. We examined the abstracts of the remaining fourteen articles. Systematic reviews and study protocols for future health economic analyses were excluded. Eventually, five articles were deemed relevant for inclusion. Table 39 provides an overview of the five articles, including the context of the screening program, the method applied, the outcomes that were measured, and what those outcomes were.

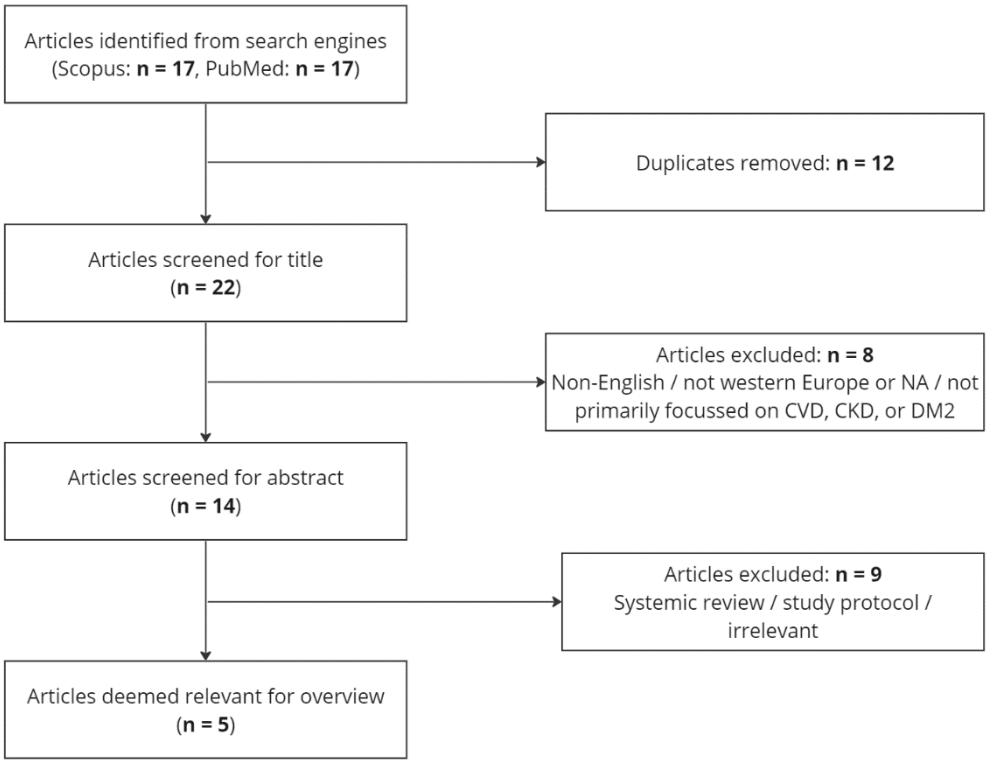



**Figure 12.** Selection procedure previous health economic evaluations

Two health economic evaluations focused on population screening for AF, two on population screening for CVD in general, and one on population screening for CKD. No health economic evaluations on population screening for DM2 were found between 2016 and September 2023. All five health economic evaluations claimed that population screening for the corresponding disease was cost-effective or cost-saving. Furthermore, the studies reporting CVD-events, showed that population screening resulted in a reduction in CVD-events. In our search, no health economic evaluations on population screening combining CVD, CKD, and DM2 were found. Therefore, to our knowledge, Check@Home is the first home-based screening program focusing on a combination of CVD (i.e., AF, CAD, HF), CKD, and DM2 in the Netherlands and beyond.

**Table 39.** Overview previous health economic evaluations

| Reference | Disease | General Description / Context | Methodology | Measured Outcomes |
|---|---|---|---|---|
| (Lyth et al., 2023) | AF | Cost-effectiveness of a population-based AF screening program in Sweden. The evaluated screening program consisted of screening of 75/76-year-old individuals. The participant were equipped with handheld ECG recorder at home (i.e., Zenicor-EKG). The participants were instructed to perform 30 seconds recordings twice daily for 2 weeks. | • State-transition model (cohort-based);<br>• Monte-Carlo simulations (PSA);<br>• Lifetime horizon;<br>• Only presence of AF was modelled. AF progression was not included;<br>• Societal perspective (excluding productivity loss). | • Number of strokes, systemic embolisms, bleedings;<br>• Cost per QALY gained;<br>• Cost per life year gained.<br>• Outcome: AF screening strategy in elderly people is cost-effective. Screening 1,000 individuals results in 10.6 fewer strokes, 1.0 more cases of systemic embolism, and 2.9 fewer bleedings. Cost per QALY gained: - € 27,156 (dominant). Cost per life years gained: - € 23,011 (dominant). 99.2% cost-effective and 92.7% cost saving. |
| (Proietti et al., 2019) | AF | Cost-effectiveness and screening performance of a population-based AF screening program with handheld ECG recorder. The target population matched the population of the Belgium Heart Rhythm Week (BHRW) screening study. Simulations were performed for the overall population of adults, as well as subgroups of subjects ≥ 65 years and ≥ 75 years. One week per year the Belgium Heart Association organizes the BHRW, a national AF screening campaign. Subjects were invited to attend the screening procedure and perform a clinical questionnaire. | • State-transition model (cohort-based);<br>• Lifetime horizon;<br>• Screening once a year during BHRW;<br>• CHA2DS2-VASc score was used to asses the risk of stroke;<br>• Perspective: not reported. | • Number of detected AF<br>• Number of strokes<br>• Cost per QALY gained;<br>• Cost per life year gained.<br>• Outcome - General population: 2.8 less strokes per 1,000 individuals / €11,788 per life years gained / €24,345 per QALY gained;<br>• Outcome – population ≥ 65 years: 2.9 less strokes per 1,000 individuals / €19,378 per life years gained / €17,693 per QALY gained;<br>• Outcomes – population ≥ 75 years: 2.7 less strokes per 1,000 individuals / €5,876 per life years gained / €6,708 per QALY gained. |
| (Søgaard et al., 2022) | CVD (AF and CAD included) | Cost-effectiveness of screening men for CVD versus usual practice of no screening in Denmark. Men aged between 65 and 74 living in 15 municipalities in Denmark were included. Once invited, participates were asked to book a time slot. The screening program consisted of: A multimodal screening test package including low dose computed tomography (CT) to detect coronary artery calcification, four limb blood pressure measurement to detect PAD and hypertension, telemetric assessment of the heart rhythm to detect atrial fibrillation, and measurements of cholesterol and HbA1c levels. | • No health economic model was developed. Instead, the article conducted a 1:2 randomized controlled trial comparing population screening for CVD with no population screening;<br>• 7.3-years of follow-up;<br>• Societal perspective (including patient- and family costs). | • Cost per life years gained;<br>• Cost per QALY gained;<br>• Outcome: €10,812 per life years gained and €9,075 per QALY gained. At a WTP-threshold of €20,000, screening men for CVD is cost-effective at probability 0.73 (cost per QALY). |

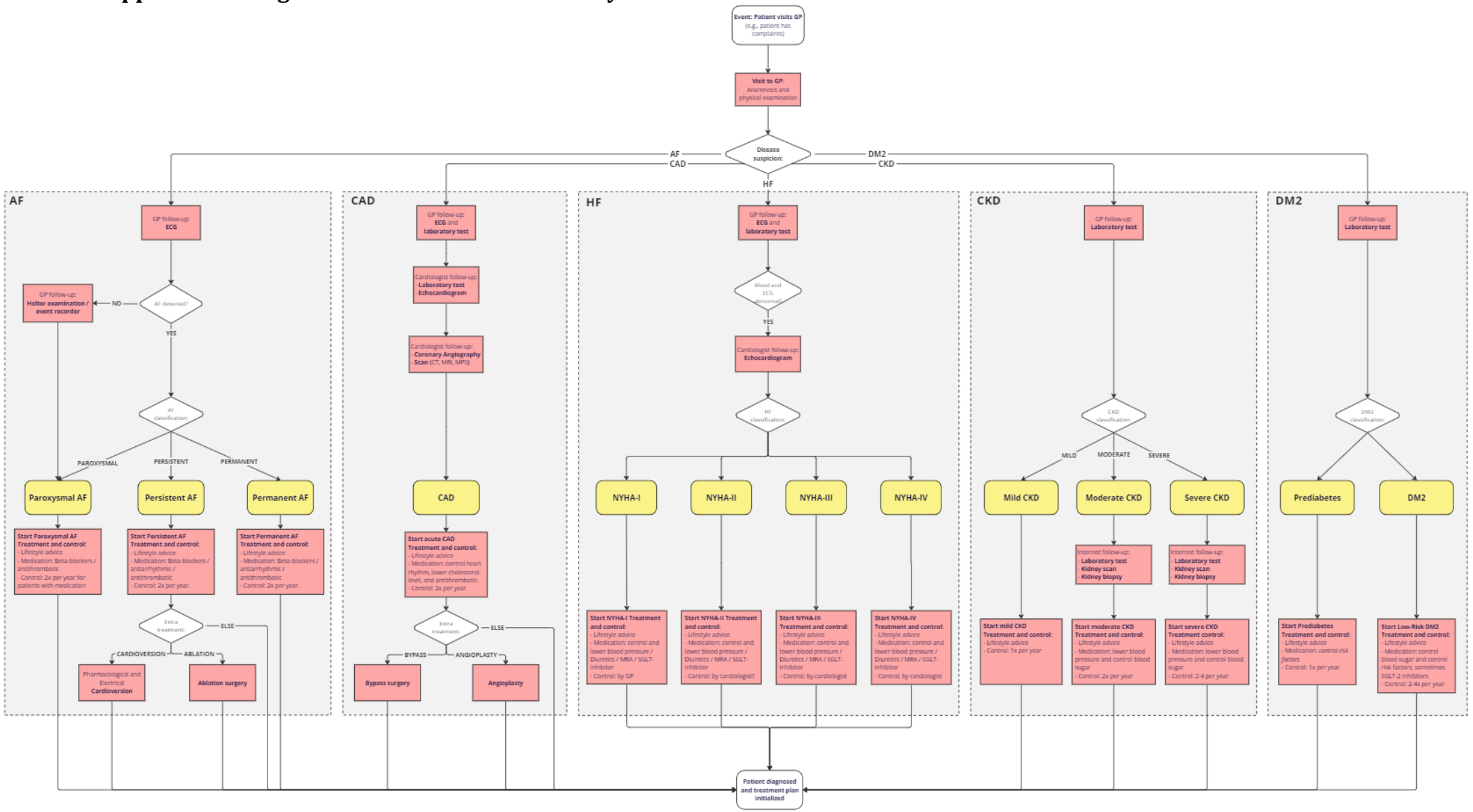
| | | | | |
|---|---|---|---|---|
| (Jülicher & Varounis, 2022) | CVD | Cost-effectiveness of general population screening for cardiovascular risk with high-sensitivity troponin-I test (hsTpI test). The study evaluated a low risk (Germany) and high-risk (Kazakhstan) country. They compared a Screen&Prevent strategy in a population aged 40-65 with a do nothing strategy. Patients who were considered high risk after the hsTpI-test received medical therapy (i.e., statin). High levels of hsTpI are associated with more severe CAD. | • Individual-level discrete-event simulation model.<br>• 10-years time horizon.<br>• The model simulated whether a CVD-event occurred during the follow-up time. In case of a non-fatal event, individuals moved into a post-CVD state until they died either from CVD or any other causes, or they exited the model after the end of the time horizon. | • Number of CVD-events<br>• Cost per QALY gained<br>• Direct and indirect costs<br>• Outcome: In the Screen&Prevent strategy, the number of CVD-events per 1,000 subjects were reduced by 5.1 and 5.0 in Kazakhstan and Germany respectively. Screen&Prevent was cost saving in Kazakhstan and cost-effective in Germany with an ICER of $6,755 per QALY gained. |
| (Pouwels et al., 2023; van Mil et al., 2023) | CKD | Cost-effectiveness of home-based population screening to detect undiagnosed CKD and risk factors for progression and CVD. The target population include individuals aged 45-80 years. The two screening methods are the urine collection device (UCD) and APP-method. The THOMAS study is still ongoing. | • State-transition model (individual-based);<br>• Lifetime horizon;<br>• CKD progression: Based on decrease in eGFR and albuminuria progression / regression;<br>• Healthcare perspective. | • Cost per QALY gained<br>• Preliminary results THOMAS study (UCD versus usual care): home-based population screening with a UCD is cost-effective with an ICER of € 9,204. |

## Appendix 5: Set of Events

**Table 40.** Set of events per type of individual.

| | Individual/Patient Type | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Event** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** | **14** | **15** | **16** | **17** | **18** | **19** | **20** | **21** | **22** | **23** | **24** | **25** | **26** | **27** | **28** | **29** |
| 1. Diagnosis through standard care | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 0 | 1 | 1 |
| 2. AF Disease Development | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3. CAD Disease Development | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 4. HF Disease Development | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 5. CKD Disease Development | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6. DM2 Disease Development | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 7. Progress paroxysmal to persistent AF | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8. Progress persistent to permanent AF | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 10. Progress NYHA-I to NYHA-II | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 11. Progress NYHA-II to NYHA-III | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12. Progress NYHA-III to NYHA-IV | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 13. Progress mild to moderate CKD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 14. Progress moderate to severe CKD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 |
| 15. Progress severe CKD to ESRD | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| 16. Progress prediabetes to DM2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 |
| 17. Transient Ischemic Attack (TIA) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 18. CVD-event (i.e., IS, HS, MI, CA, aHF) | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 19. Background mortality | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |

## Appendix 6: Diagnostic and Treatment Pathway



## Appendix 7: Explanation Input Parameters for Patient Characteristics

Table 41 presents the inputs used at model initiation for the characteristics gender, age, smoking status, TC level, HDL level and SBP.

*Gender, Age, and Smoking Status*

To determine the gender and age of a new individual, we used general population data from the Dutch National Statistics (CBS, 2021), by looking at men and women aged 50-75 years old. Whether the new individual smokes or not depend on the gender of the individual. According to data from the Ministry of Health, Welfare, and Sports (VZinfo, 2023), 17.2% of men and 12.4% of women smoke over 50 years of age. In our DES model, we assumed that the smoke-status is fixed over the lifetime of the individual.

*Cholesterol levels*

Balder et al. (2017) studied the age- and gender-specific lipid values from 133,450 Dutch lifeline participants. To determine the total cholesterol level (TC-level) and high-density lipoprotein cholesterol level (HDL-level), we used the 1st, 2.5th, 5th, 10th, 25th, 50th, 75th, 90th, 95th, 97.5th, and 99th age- and gender-specific percentile values as provided by Balder et al. (2017). Subsequently, we fitted a normal distribution to the percentile values. To convert the TC-level and HDL-level from mg/dL to mmol/L, a conversion rate of 0.02586 was used (Balder et al., 2017). The results (in mg/dL) are shown in Table 39.

*Systolic Blood Pressure*

The RIVM (2012) published evidence about the mean systolic blood pressure (SBP) in mmHg by gender and age category in the Netherlands in 2010. The data is presented in Table 39 and was used to determine the SBP of individuals in our DES model. We assumed that the SBP in people aged older than 70 years follow the same normal distribution as people aged 60-70 years.

**Table 41.** Baseline population characteristics for gender, age, smoking status, TC level, HDL level and SBP

| **Gender** | | | | | |
|---|---|---|---|---|---|
| | *Prob. (%)* | | | | *Source* |
| Men | 49.73 % | | | | (CBS, 2021) |
| Women | 50.27 % | | | | (CBS, 2021) |
| **Age** | | | | | |
| | **Men** | **Women** | | | |
| | *Prob. (%)* | *Prob. (%)* | | | *Source* |
| Aged 50-54 | 22.90 % | 22.53 % | | | (CBS, 2021) |
| Aged 55-59 | 22.51 % | 22.12 % | | | (CBS, 2021) |
| Aged 60-64 | 20.13 % | 20.06 % | | | (CBS, 2021) |
| Aged 65-69 | 17.62 % | 17.83 % | | | (CBS, 2021) |
| Aged 70-74 | 16.84 % | 17.46 % | | | (CBS, 2021) |
| **Smoking Status** | | | | | |
| | **Men** | **Women** | | | |
| | *Prob. (%)* | *Prob. (%)* | | | *Source* |
| Smoker | 17.18 % | 12.39 % | | | (VZinfo, 2023) |
| Non-Smoker | 82.82 % | 87.61 % | | | (VZinfo, 2023) |
| **TC-Level** | | | | | |
| | **Men** | | **Women** | | |
| *Age category* | *Mean (mg/dL)* | *Sd. (mg/dL)* | *Mean (mg/dL)* | *Sd. (mg/dL)* | *Source* |
| Aged 50-54 | 215.1 | 33.7 | 217.3 | 34.1 | (Balder et al., 2017) |
| Aged 55-59 | 216.3 | 33.1 | 228.9 | 34.8 | (Balder et al., 2017) |
| Aged 60-64 | 214.8 | 33.2 | 232.6 | 33.9 | (Balder et al., 2017) |
| Aged 65-69 | 214.5 | 32.9 | 235.1 | 34.4 | (Balder et al., 2017) |
| Aged 70-74 | 211.7 | 34.1 | 232.1 | 34.0 | (Balder et al., 2017) |
| Aged 75-79 | 209.1 | 33.0 | 227.6 | 32.9 | (Balder et al., 2017) |
| Aged 80+ | 205.0 | 31.0 | 228.7 | 32.0 | (Balder et al., 2017) |
| **HDL-Level** | | | | | |
| | **Men** | | **Women** | | |
| Age category | *Mean (mg/dL)* | *Sd. (mg/dL)* | *Mean (mg/dL)* | *Sd. (mg/dL)* | *Source* |
| Aged 50-54 | 50.9 | 10.8 | 66.3 | 16.3 | (Balder et al., 2017) |
| Aged 55-59 | 52.3 | 12.5 | 66.3 | 16.3 | (Balder et al., 2017) |
| Aged 60-64 | 52.3 | 12.5 | 66.4 | 16.1 | (Balder et al., 2017) |
| Aged 65-69 | 54.4 | 12.1 | 66.3 | 16.3 | (Balder et al., 2017) |
| Aged 70-74 | 54.4 | 12.1 | 64.9 | 16.1 | (Balder et al., 2017) |
| Aged 75-79 | 54.4 | 12.1 | 66.3 | 16.3 | (Balder et al., 2017) |
| Aged 80+ | 52.2 | 12.8 | 66.2 | 16.0 | (Balder et al., 2017) |
| **Systolic Blood Pressure** | | | | | |
| | **Men** | | **Women** | | |
| *Age category* | *Mean (mmHg)* | *Sd. (mmHg)* | *Mean (mmHg)* | *Sd. (mmHg)* | *Source* |
| Aged 50-59 | 136 | 15 | 127 | 17 | (RIVM, 2012) |
| Aged 60-69 | 143 | 20 | 137 | 20 | (RIVM, 2012) |
| Aged 70+ | 143 | 20 | 137 | 20 | (RIVM, 2012) |

# Appendix 8: Probabilistic Sensitivity Analysis – Parameter Distributions

| **Parameters at model initiation** | | | | |
|---|---|---|---|---|
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Probability Paroxysmal AF (stage distr.) | Dirichlet | Alpha: (2606, 2341, 4869) | - | (Chiang et al., 2012) |
| Probability Persistent AF (stage distr.) | | | | (Chiang et al., 2012) |
| Probability Permanent AF (stage distr.) | | | | (Chiang et al., 2012) |
| Probability NYHA-I (stage distr.) | Dirichlet | Alpha: (14896, 39815, 41758, 16128) | - | (Norhammar et al., 2023) |
| Probability NYHA-II (stage distr.) | | | | (Norhammar et al., 2023) |
| Probability NYHA-III (stage distr.) | | | | (Norhammar et al., 2023) |
| Probability NYHA-IV (stage distr.) | | | | (Norhammar et al., 2023) |
| Probability CKD in men aged 50-54 | Beta | Mean: 0.010 | Sd: 0.001 | (van Blijderveen et al., 2014) |
| Probability CKD in men aged 55-59 | Beta | Mean: 0.021 | Sd: 0.002 | (van Blijderveen et al., 2014) |
| Probability CKD in men aged 60-64 | Beta | Mean: 0.043 | Sd: 0.003 | (van Blijderveen et al., 2014) |
| Probability CKD in men aged 65-69 | Beta | Mean: 0.084 | Sd: 0.004 | (van Blijderveen et al., 2014) |
| Probability CKD in men aged 70-75 | Beta | Mean: 0.152 | Sd: 0.006 | (van Blijderveen et al., 2014) |
| Probability CKD in women aged 50-54 | Beta | Mean: 0.022 | Sd: 0.002 | (van Blijderveen et al., 2014) |
| Probability CKD in women aged 55-59 | Beta | Mean: 0.039 | Sd: 0.003 | (van Blijderveen et al., 2014) |
| Probability CKD in women aged 60-64 | Beta | Mean: 0.073 | Sd: 0.003 | (van Blijderveen et al., 2014) |
| Probability CKD in women aged 65-69 | Beta | Mean: 0.125 | Sd: 0.005 | (van Blijderveen et al., 2014) |
| Probability CKD in women aged 70-75 | Beta | Mean: 0.212 | Sd: 0.007 | (van Blijderveen et al., 2014) |
| Probability Mild CKD (stage distr.) | Dirichlet | Alpha: (31541, 13089, 9258, 208) | - | (Leemrijse et al., 2021) |
| Probability Moderate CKD (stage distr.) | | | | (Leemrijse et al., 2021) |
| Probability Severe CKD (stage distr.) | | | | (Leemrijse et al., 2021) |
| Probability Kidney Failure (stage distr.) | | | | (Leemrijse et al., 2021) |
| Probability Prediabetes in men aged 45-54 | Beta | Mean: 0.10 | Sd: 0.05 | (van Herpt et al., 2020) |
| Probability Prediabetes in men aged 55-64 | Beta | Mean: 0.20 | Sd: 0.04 | (van Herpt et al., 2020) |
| Probability Prediabetes in men aged 65-75 | Beta | Mean: 0.19 | Sd: 0.04 | (van Herpt et al., 2020) |
| Probability Prediabetes in women aged 45-54 | Beta | Mean: 0.06 | Sd: 0.05 | (van Herpt et al., 2020) |
| Probability Prediabetes in women aged 55-64 | Beta | Mean: 0.13 | Sd: 0.05 | (van Herpt et al., 2020) |
| Probability Prediabetes in women aged 65-75 | Beta | Mean: 0.19 | Sd: 0.05 | (van Herpt et al., 2020) |
| **Probabilities: Interventions** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Probability Cardioversion (AF patients) | Beta | Mean: 0.656 | Sd: 0.1312 | Assumption |
| Probability Ablation Surgery (AF patients) | Beta | Mean: 0.066 | Sd: 0.0132 | Assumption |
| Probability Angioplasty (CAD patients) | Beta | Mean: 0.400 | Sd: 0.080 | Assumption |
| Probability Bypass surgery (CAD patients) | Beta | Mean: 0.050 | Sd: 0.010 | Assumption |
| **Control Visits** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Nr of GP visits per year: AF patients | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2017) |
| Nr of GP visits per year: CAD patients | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2022) |
| Nr of hospital visits per year: CAD patients | Gamma | Mean: 1 | Sd: 0.200 | (NHG, 2022) |
| Nr of GP visits per year: NYHA-I patients | Gamma | Mean: 1 | Sd: 0.200 | (NHG, 2018) |
| Nr of GP visits per year: NYHA-II patients | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2018) |
| Nr of GP visits per year: NYHA-III patients | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2018) |
| Nr of hospital visits per year: NYHA-III patients | Gamma | Mean: 1 | Sd: 0.200 | (NHG, 2018) |
| Nr of GP visits per year: NYHA-IV patients | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2018) |
| Nr of hospital visits per year: NYHA-IV patients | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2018) |
| Nr of GP visits per year: mild CKD | Gamma | Mean: 1 | Sd: 0.200 | (NHG, 2021) |
| Nr of GP visits per year: moderate CKD | Gamma | Mean: 2 | Sd: 0.400 | (NHG, 2021) |
| Nr of hospital visits per year: moderate CKD | Gamma | Mean: 1 | Sd: 0.200 | (NHG, 2021) |
| Nr of GP visits per year: Prediabetes | Gamma | Mean: 1 | Sd: 0.200 | Assumption |
| Nr of GP visits per year: TIA (without treatment yet) | Gamma | Mean: 1 | Sd: 0.200 | Assumption |
| **Costs** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Annual Cost Severe CKD | Gamma | Shape: 2097051 | Scale: 0.005688 | (van Oosten et al., 2020) |
| Annual Cost Kidney Failure | Gamma | Shape: 2097051 | Scale: 0.005688 | (van Oosten et al., 2020) |
| Annual Cost DM2 | Gamma | Mean: 6978 | Sd: 1395.6 | (S. A. G. de Vries et al., 2023) |
| Annual Cost Dialysis | Gamma | Shape: 28546661 | Scale: 0.003964 | (Mohnen et al., 2019) |

| | | | | |
|---|---|---|---|---|
| Cost kidney transplantation: Year 1 | Gamma | Shape: 11405389 | Scale: 0.008763 | (Mohnen et al., 2019) |
| Cost kidney transplantation: Year 2 | Gamma | Shape: 1289895 | Scale: 0.026955 | (Mohnen et al., 2019) |
| Cost kidney transplantation: Year 3+ | Gamma | Shape: 541852 | Scale: 0.043676 | (Mohnen et al., 2019) |
| Cost conservative treatment (ESRD) | Gamma | Mean: 14260 | Sd: 2852 | (Gardiner et al., 2018) |
| Acute cost IS (recovered patients) | Gamma | Mean: 20448 | Sd: 4090 | (van Hulst et al., 2022) |
| Annual cost IS (recovered patients) | Gamma | Mean: 6340 | Sd: 1268 | (van Hulst et al., 2022) |
| Acute cost IS (not recovered patients) | Gamma | Mean: 47139 | Sd: 9428 | (van Hulst et al., 2022) |
| Annual cost IS (not recovered patients) | Gamma | Mean: 16908 | Sd: 3382 | (van Hulst et al., 2022) |
| Death IS | Gamma | Mean: 11938 | Sd: 2388 | (van Hulst et al., 2022) |
| Acute cost HS (recovered patients) | Gamma | Mean: 25944 | Sd: 5189 | (van Hulst et al., 2022) |
| Annual cost HS (recovered patients) | Gamma | Mean: 7224 | Sd: 1445 | (van Hulst et al., 2022) |
| Acute cost HS (not recovered patients) | Gamma | Mean: 47139 | Sd: 9428 | Assumption |
| Annual cost HS (not recovered patients) | Gamma | Mean: 16908 | Sd: 3382 | Assumption |
| Death HS | Gamma | Mean: 6448 | Sd: 1290 | (van Hulst et al., 2022) |
| Acute cost MI | Gamma | Mean: 5362 | Sd: 1072 | (van Hulst et al., 2022) |
| Annual cost MI | Gamma | Mean: 1196 | Sd: 239 | (van Hulst et al., 2022) |
| Death MI | Gamma | Mean: 5362 | Sd: 1072 | Assumption |
| Acute cost CA (recovered patients) | Gamma | Mean: 5362 | Sd: 1072 | Assumption |
| Annual cost CA (recovered patients) | Gamma | Mean: 1196 | Sd: 239 | Assumption |
| Acute cost CA (not recovered patients) | Gamma | Mean: 5362 | Sd: 1072 | Assumption |
| Annual cost CA (not recovered patients) | Gamma | Mean: 1196 | Sd: 239 | Assumption |
| Death CA | Gamma | Mean: 5362 | Sd: 1072 | Assumption |
| Death acute HF | Gamma | Mean: 5704 | Sd: 1141 | (Stevanovic et al., 2014) |
| TIA (acute cost) | Gamma | Mean: 3057 | Sd: 611 | (Buisman et al., 2015) |
| **Utilities** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Healthy individuals aged 50-59 | Beta | Mean: 0.857 | Sd: 0.183 | (Versteegh et al., 2016) |
| Healthy individuals aged 60-69 | Beta | Mean: 0.839 | Sd: 0.179 | (Versteegh et al., 2016) |
| Healthy individuals aged 70+ | Beta | Mean: 0.852 | Sd: 0.148 | (Versteegh et al., 2016) |
| Paroxysmal AF – men | Beta | Mean: 0.790 | Sd: 0.230 | (Doyle et al., 2011) |
| Persistent AF – men | Beta | Mean: 0.800 | Sd: 0.210 | (Doyle et al., 2011) |
| Permanent AF – men | Beta | Mean: 0.730 | Sd: 0.260 | (Doyle et al., 2011) |
| Stable CAD | Beta | Mean: 0.671 | Sd: 0.046 | (Petersohn et al., 2020) |
| HF – NYHA-I | Beta | Mean: 0.855 | Sd: 0.005 | (Göhler et al., 2009) |
| HF – NYHA-II | Beta | Mean: 0.771 | Sd: 0.005 | (Göhler et al., 2009) |
| HF – NYHA-III | Beta | Mean: 0.673 | Sd: 0.006 | (Göhler et al., 2009) |
| HF – NYHA-IV | Beta | Mean: 0.532 | Sd: 0.027 | (Göhler et al., 2009) |
| Mild CKD | Beta | Mean: 0.800 | Sd: 0.079 | (Cooper et al., 2020) |
| Moderate CKD | Beta | Mean: 0.800 | Sd: 0.082 | (Cooper et al., 2020) |
| Severe CKD | Beta | Mean: 0.740 | Sd: 0.059 | (Cooper et al., 2020) |
| Kidney Failure (ESRD) | Beta | Mean: 0.570 | Sd: 0.330 | (Lee et al., 2005) |
| Dialysis | Beta | Mean: 0.440 | Sd: 0.320 | (Lee et al., 2005) |
| Post Kidney Transplantation | Beta | Mean: 0.710 | Sd: 0.270 | (Lee et al., 2005) |
| DM2 | Beta | Mean: 0.815 | Sd: 0.004 | (Redenz et al., 2023) |
| Stroke (IS/HS): Recovered (month: 0-3) | Beta | Mean: 0.655 | Sd: 0.044 | (van Hulst et al., 2022) |
| Stroke (IS/HS): Recovered (month : 3+) | Beta | Mean: 0.752 | Sd: 0.052 | (van Hulst et al., 2022) |
| Stroke (IS/HS): Not Recovered (month: 0-3) | Beta | Mean: 0.167 | Sd: 0.009 | (van Hulst et al., 2022) |
| Stroke (IS/HS): Not Recovered (month: 3+) | Beta | Mean: 0.449 | Sd: 0.028 | (van Hulst et al., 2022) |
| Decrement for MI | Trunc. Normal | Mean: -0.0557 | Sd: 0.0112 | (van Hulst et al., 2022) |
| Decrement for CA | Trunc. Normal | Mean: -0.0557 | Sd: 0.0112 | Assumption |
| **Hazard Ratios** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| AF increased CVD risk | Log-Normal | Meanlog: 0.67 | Sdlog: 0.13 | (Odutayo et al., 2016) |
| HF: NYHA-I increased CVD risk | Fixed | 1.00 | | Assumption |
| HF: NYHA-II increased CVD risk | Log-Normal | Meanlog: 0.43 | Sdlog: 0.21 | (Ahmed et al., 2006) |
| HF: NYHA-III increased CVD risk | Log-Normal | Meanlog: 0.94 | Sdlog: 0.23 | (Ahmed et al., 2006) |
| HF: NYHA-IV increased CVD risk | Log-Normal | Meanlog: 2.14 | Sdlog: 0.44 | (Ahmed et al., 2006) |
| Prediabetes increased CVD risk | Log-Normal | Meanlog: 0.12 | Sdlog: 0.02 | (Mando et al. 2021) |
| Calcium Antagonists | Log-Normal | Meanlog: - 0.24 | Sdlog: 0.11 | (Turnbull et al., 2005) |
| Antithrombotics | Log-Normal | Meanlog: - 0.30 | Sdlog: 0.07 | (Connolly et al., 2018) |
| Statin | Log-Normal | Meanlog: - 0.29 | Sdlog: 0.04 | (Taylor et al., 2013) |
| ACE-inhibitors | Log-Normal | Meanlog: - 0.34 | Sdlog: 0.08 | (Wei et al., 2020) |

| | | | | |
|---|---|---|---|---|
| SGLT2-inhibitors | Log-Normal | Meanlog: - 0.24 | Sdlog: 0.09 | (Tsai et al., 2022) |
| AF progression | Fixed | 1.00 | | Assumption |
| HF progression | Log-Normal | Meanlog: - 0.34 | Sdlog: 0.08 | (Wei et al., 2020) |
| CKD progression: mild to moderate | Log-Normal | Meanlog: - 0.34 | Sdlog: 0.08 | (Wei et al., 2020) |
| CKD progression | Log-Normal | Meanlog: - 0.45 | Sdlog: 0.13 | (Heerspink et al., 2020) |
| DM2 progression | Log-Normal | Meanlog: - 0.67 | Sdlog: 0.08 | (Gossain & Aldasouqi, 2010) |
| **Probabilities: Progression** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Progression: AF | Beta | Shape 1: 1479 | Shape 2: 4756 | (Holmqvist et al., 2015) |
| Progression: HF to one NYHA class higher | Beta | Shape 1: 225 | Shape 2: 3962 | (Wei et al., 2020; Zueger et al., 2018) |
| Progression: mild to moderate CKD | Beta | Mean: 0.1009 | Sd: 0.0202 | (Elbasha et al., 2017) |
| Progression: moderate to severe CKD | Beta | Shape 1: 228.42 | Shape 2: 1438.88 | (Elbasha et al., 2017) |
| Progression: severe CKD to ESRD | Beta | Shape 1: 110.09 | Shape 2: 1249.03 | (Elbasha et al., 2017) |
| Progression: PreDM2 to DM2: 10-y risk at age 55 | Beta | Mean: 0.342 | Sd: 0.058 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: 10-y risk at age 65 | Beta | Mean: 0.355 | Sd: 0.031 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: 10-y risk at age 75 | Beta | Mean: 0.393 | Sd: 0.034 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: 10-y risk at age 85 | Beta | Mean: 0.211 | Sd: 0.041 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: life risk at age 55 | Beta | Mean: 0.742 | Sd: 0.029 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: life risk at age 65 | Beta | Mean: 0.619 | Sd: 0.028 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: life risk at age 75 | Beta | Mean: 0.491 | Sd: 0.034 | (van Herpt et al., 2020) |
| Progression: PreDM2 to DM2: life risk at age 85 | Beta | Mean: 0.211 | Sd: 0.041 | (van Herpt et al., 2020) |
| **Probabilities: Disease Development** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Lifetime risk AF: Men aged 55 | Beta | Mean: 0.238 | Sd: 0.029 | (Heeringa et al., 2006) |
| Lifetime risk AF: Men aged 60 | Beta | Mean: 0.233 | Sd: 0.029 | (Heeringa et al., 2006) |
| Lifetime risk AF: Men aged 65 | Beta | Mean: 0.227 | Sd: 0.029 | (Heeringa et al., 2006) |
| Lifetime risk AF: Men aged 70 | Beta | Mean: 0.219 | Sd: 0.030 | (Heeringa et al., 2006) |
| Lifetime risk AF: Men aged 75 | Beta | Mean: 0.202 | Sd: 0.032 | (Heeringa et al., 2006) |
| Lifetime risk AF: Men aged 80 | Beta | Mean: 0.161 | Sd: 0.035 | (Heeringa et al., 2006) |
| Lifetime risk AF: Men aged 85 | Beta | Mean: 0.118 | Sd: 0.041 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 55 | Beta | Mean: 0.222 | Sd: 0.026 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 60 | Beta | Mean: 0.223 | Sd: 0.026 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 65 | Beta | Mean: 0.221 | Sd: 0.026 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 70 | Beta | Mean: 0.211 | Sd: 0.027 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 75 | Beta | Mean: 0.183 | Sd: 0.028 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 80 | Beta | Mean: 0.153 | Sd: 0.029 | (Heeringa et al., 2006) |
| Lifetime risk AF: Women aged 85 | Beta | Mean: 0.118 | Sd: 0.031 | (Heeringa et al., 2006) |
| 5-year risk CKD: Men aged 55 | Beta | Mean: 0.012 | Sd: 0.003 | (Inker et al., 2015) |
| 10-year risk CKD: Men aged 55 | Beta | Mean: 0.032 | Sd: 0.005 | (Inker et al., 2015) |
| 20-year risk CKD: Men aged 55 | Beta | Mean: 0.111 | Sd: 0.009 | (Inker et al., 2015) |
| 30-year risk CKD: Men aged 55 | Beta | Mean: 0.207 | Sd: 0.013 | (Inker et al., 2015) |
| 5-year risk CKD: Men aged 65 | Beta | Mean: 0.027 | Sd: 0.005 | (Inker et al., 2015) |
| 10-year risk CKD: Men aged 65 | Beta | Mean: 0.090 | Sd: 0.009 | (Inker et al., 2015) |
| 20-year risk CKD: Men aged 65 | Beta | Mean: 0.198 | Sd: 0.014 | (Inker et al., 2015) |
| 5-year risk CKD: Men aged 75 | Beta | Mean: 0.082 | Sd: 0.011 | (Inker et al., 2015) |
| 10-year risk CKD: Men aged 75 | Beta | Mean: 0.139 | Sd: 0.016 | (Inker et al., 2015) |
| 5-year risk CKD: Men aged 80 | Beta | Mean: 0.074 | Sd: 0.015 | (Inker et al., 2015) |
| 10-year risk CKD: Men aged 80 | Beta | Mean: 0.104 | Sd: 0.020 | (Inker et al., 2015) |
| 5-year risk CKD: Women aged 55 | Beta | Mean: 0.020 | Sd: 0.004 | (Inker et al., 2015) |
| 10-year risk CKD: Women aged 55 | Beta | Mean: 0.060 | Sd: 0.006 | (Inker et al., 2015) |
| 20-year risk CKD: Women aged 55 | Beta | Mean: 0.189 | Sd: 0.010 | (Inker et al., 2015) |
| 30-year risk CKD: Women aged 55 | Beta | Mean: 0.340 | Sd: 0.016 | (Inker et al., 2015) |
| 5-year risk CKD: Women aged 65 | Beta | Mean: 0.053 | Sd: 0.006 | (Inker et al., 2015) |
| 10-year risk CKD: Women aged 65 | Beta | Mean: 0.141 | Sd: 0.009 | (Inker et al., 2015) |
| 20-year risk CKD: Women aged 65 | Beta | Mean: 0.316 | Sd: 0.017 | (Inker et al., 2015) |
| 5-year risk CKD: Women aged 75 | Beta | Mean: 0.100 | Sd: 0.011 | (Inker et al., 2015) |
| 10-year risk CKD: Women aged 75 | Beta | Mean: 0.222 | Sd: 0.019 | (Inker et al., 2015) |
| 5-year risk CKD: Women aged 80 | Beta | Mean: 0.150 | Sd: 0.020 | (Inker et al., 2015) |
| 10-year risk CKD: Women aged 80 | Beta | Mean: 0.249 | Sd: 0.030 | (Inker et al., 2015) |
| 10-year risk DM2: Aged 55 | Beta | Mean: 0.132 | Sd: 0.009 | (Ligthart et al., 2016) |
| 10-year risk DM2: Aged 65 | Beta | Mean: 0.193 | Sd: 0.008 | (Ligthart et al., 2016) |

| | | | | |
|---|---|---|---|---|
| 10-year risk DM2: Aged 75 | Beta | Mean: 0.191 | Sd: 0.009 | (Ligthart et al., 2016) |
| 10-year risk DM2: Aged 85 | Beta | Mean: 0.119 | Sd: 0.013 | (Ligthart et al., 2016) |
| Lifetime risk DM2: Aged 55 | Beta | Mean: 0.445 | Sd: 0.010 | (Ligthart et al., 2016) |
| Lifetime risk DM2: Aged 65 | Beta | Mean: 0.376 | Sd: 0.010 | (Ligthart et al., 2016) |
| Lifetime risk DM2: Aged 75 | Beta | Mean: 0.258 | Sd: 0.011 | (Ligthart et al., 2016) |
| Lifetime risk DM2: Aged 85 | Beta | Mean: 0.131 | Sd: 0.014 | (Ligthart et al., 2016) |
| **Probabilities: Visit GP to get diagnosed** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Probability diagnosed: low stages | Uniform | Min: 0.05 | Max: 0.15 | Assumption |
| Probability diagnosed: middle stages | Uniform | Min: 0.45 | Max: 0.55 | Assumption |
| Probability diagnosed: high stages | Uniform | Min: 0.80 | Max: 0.90 | Assumption |
| **Probabilities: CVD-type** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| IS | Dirichlet | Alpha: (35936, 8070, 39798, 4984, 7139) | - | (CBS, 2023b, 2023c) |
| HS | | | | (CBS, 2023b, 2023c) |
| MI | | | | (CBS, 2023b, 2023c) |
| CA | | | | (CBS, 2023b, 2023c) |
| aHF | | | | (CBS, 2023b, 2023c) |
| **Probabilities: Fatal / Non-fatal CVD-event** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Fatal: IS aged 50-54 | Beta | Mean: 0.045 | Sd: 0.009 | (Hartstichting, 2021) |
| Fatal: IS aged 55-74 | Beta | Mean: 0.065 | Sd: 0.013 | (Hartstichting, 2021) |
| Fatal: IS aged 75-84 | Beta | Mean: 0.126 | Sd: 0.025 | (Hartstichting, 2021) |
| Fatal: IS aged ≥ 85 | Beta | Mean: 0.260 | Sd: 0.052 | (Hartstichting, 2021) |
| Fatal: HS aged 50-54 | Beta | Mean: 0.234 | Sd: 0.047 | (Hartstichting, 2021) |
| Fatal: HS aged 55-74 | Beta | Mean: 0.278 | Sd: 0.056 | (Hartstichting, 2021) |
| Fatal: HS aged 75-84 | Beta | Mean: 0.402 | Sd: 0.080 | (Hartstichting, 2021) |
| Fatal: HS aged ≥ 85 | Beta | Mean: 0.536 | Sd: 0.107 | (Hartstichting, 2021) |
| Fatal: MI aged 50-54 | Beta | Mean: 0.033 | Sd: 0.007 | (Hartstichting, 2021) |
| Fatal: MI aged 55-74 | Beta | Mean: 0.065 | Sd: 0.013 | (Hartstichting, 2021) |
| Fatal: MI aged 75-84 | Beta | Mean: 0.172 | Sd: 0.034 | (Hartstichting, 2021) |
| Fatal: MI aged ≥ 85 | Beta | Mean: 0.307 | Sd: 0.061 | (Hartstichting, 2021) |
| Fatal: CA aged < 70 | Beta | Shape 1: 810 | Shape 2: 347 | (Zijlstra et al., 2016) |
| Fatal: CA aged 70-80 | Beta | Shape 1: 546 | Shape 2: 124 | (Zijlstra et al., 2016) |
| Fatal: CA aged > 80 | Beta | Shape 1: 353 | Shape 2: 34 | (Zijlstra et al., 2016) |
| **Probabilities: Recover / Not recover from CVD-event** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Recover IS | Beta | Mean: 0.500 | Sd: 0.1 | (The Stroke Foundation, 2020) |
| Recover HS | Beta | Mean: 0.500 | Sd: 0.1 | (The Stroke Foundation, 2020) |
| Recover MI | Fixed | 1.000 | - | Assumption |
| Recover CA | Beta | Mean: 0.900 | Sd: 0.18 | (Zijlstra et al., 2016) |
| **Probabilities: 5-year mortality after CVD-event** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| 5-year mortality: IS aged 50-54 | Beta | Mean: 0.105 | Sd: 0.021 | (Hartstichting, 2021) |
| 5-year mortality: IS aged 55-74 | Beta | Mean: 0.262 | Sd: 0.052 | (Hartstichting, 2021) |
| 5-year mortality: IS aged 75-84 | Beta | Mean: 0.543 | Sd: 0.109 | (Hartstichting, 2021) |
| 5-year mortality: IS aged 85+ | Beta | Mean: 0.807 | Sd: 0.161 | (Hartstichting, 2021) |
| 5-year mortality: HS aged 50-54 | Beta | Mean: 0.335 | Sd: 0.067 | (Hartstichting, 2021) |
| 5-year mortality: HS aged 55-74 | Beta | Mean: 0.466 | Sd: 0.093 | (Hartstichting, 2021) |
| 5-year mortality: HS aged 75-84 | Beta | Mean: 0.725 | Sd: 0.145 | (Hartstichting, 2021) |
| 5-year mortality: HS aged 85+ | Beta | Mean: 0.883 | Sd: 0.176 | (Hartstichting, 2021) |
| 5-year mortality: MI aged 50-54 | Beta | Mean: 0.077 | Sd: 0.015 | (Hartstichting, 2021) |
| 5-year mortality: MI aged 55-74 | Beta | Mean: 0.184 | Sd: 0.037 | (Hartstichting, 2021) |
| 5-year mortality: MI aged 75-84 | Beta | Mean: 0.498 | Sd: 0.100 | (Hartstichting, 2021) |
| 5-year mortality: MI aged 85+ | Beta | Mean: 0.776 | Sd: 0.155 | (Hartstichting, 2021) |
| 5-year mortality: CA | Beta | Mean: 0.770 | Sd: 0.154 | (Zijlstra et al., 2016) |
| **Life Expectancy: Kidney dialysis and transplantation** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Life expectancy dialysis 50-54 | Trunc. Normal | Mean: 8.0 | Sd: 1.6 | Nierstichting (2022b) |

| | | | | |
|---|---|---|---|---|
| Life expectancy dialysis 55-59 | Trunc. Normal | Mean: 7.0 | Sd: 1.4 | Nierstichting (2022b) |
| Life expectancy dialysis 60-64 | Trunc. Normal | Mean: 6.0 | Sd: 1.2 | Nierstichting (2022b) |
| Life expectancy dialysis 65-69 | Trunc. Normal | Mean: 5.0 | Sd: 1.0 | Nierstichting (2022b) |
| Life expectancy dialysis 70-74 | Trunc. Normal | Mean: 4.0 | Sd: 0.8 | Nierstichting (2022b) |
| Life expectancy dialysis 75+ | Trunc. Normal | Mean: 3.0 | Sd: 0.6 | Nierstichting (2022b) |
| Life expectancy transplantation 50-54 | Trunc. Normal | Mean: 18.0 | Sd: 3.6 | Nierstichting (2022b) |
| Life expectancy transplantation 55-59 | Trunc. Normal | Mean: 15.0 | Sd: 3.0 | Nierstichting (2022b) |
| Life expectancy transplantation 60-64 | Trunc. Normal | Mean: 12.0 | Sd: 2.4 | Nierstichting (2022b) |
| Life expectancy transplantation 65-69 | Trunc. Normal | Mean: 10.0 | Sd: 2.0 | Nierstichting (2022b) |
| Life expectancy transplantation 70-74 | Trunc. Normal | Mean: 7.0 | Sd: 1.4 | Nierstichting (2022b) |
| Life expectancy transplantation 75+ | Trunc. Normal | Mean: 5.0 | Sd: 1.0 | Nierstichting (2022b) |
| **Probabilities: Screening Participation / Referral** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Participation Check@Home test | Beta | Shape 1: 4484 | Shape 2: 3068 | (van Mil et al., 2023) |
| Participation FU1 | Beta | Shape 1: 222 | Shape 2: 17 | (Pouwels et al., 2023) |
| Participation FU2 | Beta | Shape 1: 77 | Shape 2: 6 | (Pouwels et al., 2023) |
| Participation ES | Beta | Shape 1: 124 | Shape 2: 26 | (Pouwels et al., 2023) |
| Go to GP after referral | Beta | Shape 1: 54 | Shape 2: 40 | (Pouwels et al., 2023) |
| **Diagnostic Performance** | | | | |
| *Input* | *Distribution* | *Parameter* | *Parameter* | *Source* |
| Sensitivity albuminuria test | Beta | Shape 1: 113 (TP) | Shape 2: 4 (FN) | (van Mil et al., 2023) |
| Specificity albuminuria test | Beta | Shape 1: 288 (TN) | Shape 2: 8 (FP) | (van Mil et al., 2023) |
| Sensitivity AF-test | Beta | Shape 1: 104 (TP) | Shape 2: 2 (FN) | (Mol et al., 2020) |
| Specificity AF-test | Beta | Shape 1: 101 (TN) | Shape 2: 2 (FP) | (Mol et al., 2020) |
| Sensitivity Questionnaire | Beta | Mean: 0.95 | Sd: 0.025 | Assumption |
| Specificity Questionnaire | Beta | Mean: 0.95 | Sd: 0.025 | Assumption |

## Appendix 9: Stability Results

To determine the stability of the results, we ran the model for 200,000 individuals. Subsequently, for different numbers of individuals, we took 1,000 random samples of the incremental costs and incremental QALYs. Next, we determined the mean per sample and calculated the 2.5$^{th}$ and 97.5$^{th}$ percentile values. Table 42 presents the lower (2.5$^{th}$ percentile) and upper bound (97.5$^{th}$ percentile) of the incremental costs and QALYs at different numbers of individuals.

**Table 42.** Lower and upper bound of the incremental costs and incremental effects for different numbers of individuals

| # Patients | LB: incr. cost | Mean: incr. cost | UB: incr. cost | LB: incr. QALY | Mean: incr. QALY | UB: incr. QALY |
|---|---|---|---|---|---|---|
| 100 | -€ 13.444,43 | -€ 149,32 | € 13.642,88 | -0,7630 | 0,0059 | 0,7004 |
| 1000 | -€ 4.184,70 | € 0,39 | € 4.129,87 | -0,2212 | 0,0037 | 0,2361 |
| 2000 | -€ 2.966,27 | € 71,66 | € 2.686,21 | -0,1565 | 0,0075 | 0,1800 |
| 3000 | -€ 2.432,35 | -€ 24,54 | € 2.255,17 | -0,1246 | 0,0084 | 0,1546 |
| 4000 | -€ 2.106,75 | -€ 6,82 | € 2.024,43 | -0,1213 | 0,0057 | 0,1262 |
| 5000 | -€ 1.721,79 | -€ 21,84 | € 1.807,75 | -0,1023 | 0,0048 | 0,1113 |
| 7500 | -€ 1.462,50 | € 20,73 | € 1.448,90 | -0,0884 | 0,0072 | 0,0938 |
| 10000 | -€ 1.240,98 | -€ 33,58 | € 1.226,16 | -0,0663 | 0,0053 | 0,0723 |
| 15000 | -€ 995,41 | -€ 18,15 | € 1.050,98 | -0,0543 | 0,0068 | 0,0665 |
| 20000 | -€ 762,88 | € 5,97 | € 781,58 | -0,0422 | 0,0056 | 0,0504 |
| 25000 | -€ 694,27 | -€ 6,72 | € 712,90 | -0,0358 | 0,0064 | 0,0474 |
| 30000 | -€ 670,44 | -€ 12,82 | € 571,16 | -0,0289 | 0,0051 | 0,0428 |
| 35000 | -€ 583,54 | -€ 19,31 | € 549,63 | -0,0241 | 0,0064 | 0,0396 |
| 40000 | -€ 535,34 | -€ 6,86 | € 468,41 | -0,0231 | 0,0066 | 0,0363 |
| 45000 | -€ 481,82 | -€ 12,64 | € 424,64 | -0,0209 | 0,0055 | 0,0314 |
| 50000 | -€ 499,95 | -€ 8,75 | € 394,41 | -0,0182 | 0,0057 | 0,0299 |
| 55000 | -€ 376,37 | -€ 10,70 | € 354,90 | -0,0153 | 0,0062 | 0,0283 |
| 60000 | -€ 325,49 | -€ 0,85 | € 316,75 | -0,0134 | 0,0060 | 0,0240 |
| 65000 | -€ 286,81 | -€ 11,94 | € 310,09 | -0,0112 | 0,0061 | 0,0241 |
| 70000 | -€ 284,40 | -€ 15,58 | € 260,82 | -0,0097 | 0,0059 | 0,0226 |
| 75000 | -€ 245,14 | -€ 10,89 | € 236,50 | -0,0074 | 0,0059 | 0,0189 |
| 80000 | -€ 205,29 | -€ 14,62 | € 199,00 | -0,0048 | 0,0060 | 0,0174 |
| 85000 | -€ 178,88 | -€ 8,92 | € 161,98 | -0,0041 | 0,0059 | 0,0156 |
| 90000 | -€ 160,53 | -€ 14,54 | € 118,01 | -0,0019 | 0,0061 | 0,0142 |
| 95000 | -€ 113,44 | -€ 12,08 | € 93,71 | 0,0004 | 0,0059 | 0,0114 |
| 100000 | -€ 10.32 | -€ 10,32 | -€ 10.32 | 0.0060 | 0,0060 | 0.0060 |

## Appendix 10: Results - Disease Status

Table 43 presents the number of individuals per disease status at the end of the health economic model for usual care, base-case screening, optimistic screening, and pessimistic screening.

**Table 43.** Total number of individuals per disease status at the end of the simulation (n = 200,000).

| | **Usual Care** (End of the simulation) | **Base-Case screening** (End of the simulation) | **Optimistic Screening** (End of the simulation) | **Pessimistic Screening** (End of the simulation) |
|---|---|---|---|---|
| **HEALTHY** | | | | |
| Healthy Individuals | 45948 | 46083 | 45801 | 46136 |
| **AF** | | | | |
| Diagnosed Paroxysmal | 1204 | 1189 | 1178 | 1194 |
| Diagnosed Persistent | 1840 | 1803 | 1819 | 1877 |
| Diagnosed Permanent | 11238 | 11369 | 11422 | 11306 |
| Undiagnosed Paroxysmal | 2481 | 2386 | 2422 | 2379 |
| Undiagnosed Persistent | 1647 | 1609 | 1641 | 1576 |
| Undiagnosed Permanent | 1545 | 1466 | 1396 | 1501 |
| *Total* | *19955* | *19822* | *19878* | *19833* |
| **CAD** | | | | |
| Diagnosed CAD | 20956 | 21108 | 21315 | 21079 |
| Undiagnosed CAD | 4160 | 3995 | 3984 | 3993 |
| *Total* | *25116* | *25103* | *25299* | *25072* |
| **HF** | | | | |
| Diagnosed NYHA-I | 899 | 1001 | 1159 | 976 |
| Diagnosed NYHA-II | 2883 | 2941 | 3088 | 2979 |
| Diagnosed NYHA-III | 2889 | 2885 | 2848 | 2890 |
| Diagnosed NYHA-IV | 2428 | 2385 | 2383 | 2439 |
| Undiagnosed NYHA-I | 7772 | 7579 | 7625 | 7563 |
| Undiagnosed NYHA-II | 3504 | 3458 | 3420 | 3508 |
| Undiagnosed NYHA-III | 964 | 946 | 845 | 896 |
| Undiagnosed NYHA-IV | 271 | 248 | 239 | 250 |
| *Total* | *21610* | *21443* | *21607* | *21501* |
| **CKD** | | | | |
| Diagnosed Mild | 3307 | 3696 | 3787 | 3566 |
| Diagnosed Moderate | 5152 | 5347 | 5700 | 5367 |
| Diagnosed Severe | 9561 | 9741 | 9732 | 9617 |
| Diagnosed ESRD | 8169 | 8128 | 8101 | 8161 |
| Undiagnosed Mild | 8292 | 8149 | 7762 | 8026 |
| Undiagnosed Moderate | 3784 | 3720 | 3581 | 3722 |
| Undiagnosed Severe | 1540 | 1442 | 1466 | 1509 |
| Undiagnosed ESRD | 0 | 0 | 0 | 0 |
| *Total* | *39805* | *40223* | *40129* | *39968* |
| **DM2** | | | | |
| Diagnosed DM2 | 28786 | 28512 | 28550 | 28741 |
| Diagnosed Prediabetes | 2321 | 4093 | 5088 | 3488 |
| Undiagnosed DM2 | 3635 | 3118 | 2831 | 3287 |
| Undiagnosed Prediabetes | 12824 | 11603 | 10817 | 11974 |
| *Total* | *47566* | *47326* | *47286* | *47490* |

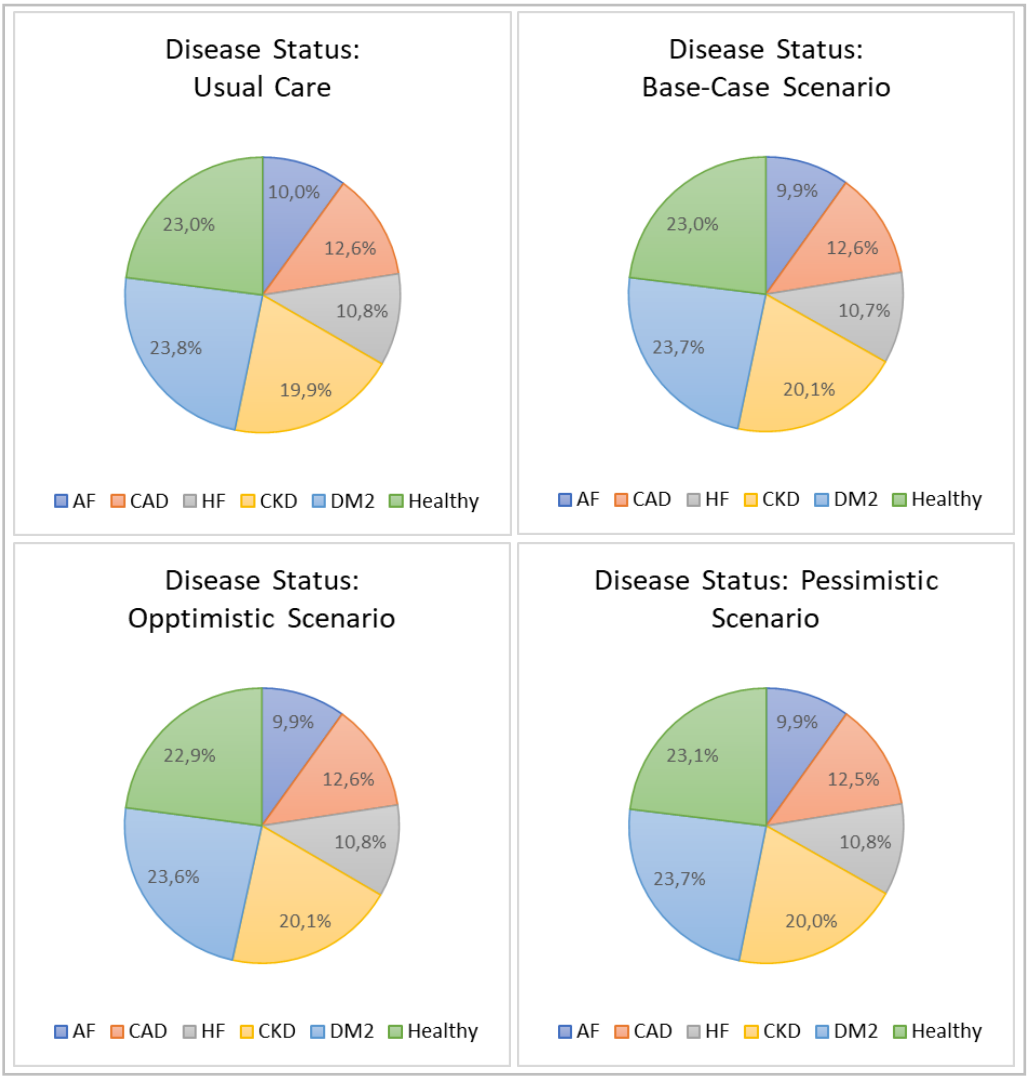



**Figure 13.** Distribution disease status per disease domain (incl. healthy status)

Figure 13 presents the (disease) status at the end of the simulation for usual care and screening in a base-case scenario, optimistic scenario, and pessimistic scenario. The proportion of the healthy group is supposed to stay relatively stable, as the risk of developing a disease is always the same.

In Figure 8 we already presented the ratio diagnosed-undiagnosed for usual care and the base-case scenario for screening. Figure 14 also presents the diagnosed-undiagnosed ration for screening in an optimistic and pessimistic scenario.

In Figure 9 we already presented the stage distribution for usual care and the base-case scenario for screening. Figure 14 also presents the stage distribution for screening in an optimistic and pessimistic scenario. The presented stage distribution, is the distribution at the end of the simulation time.

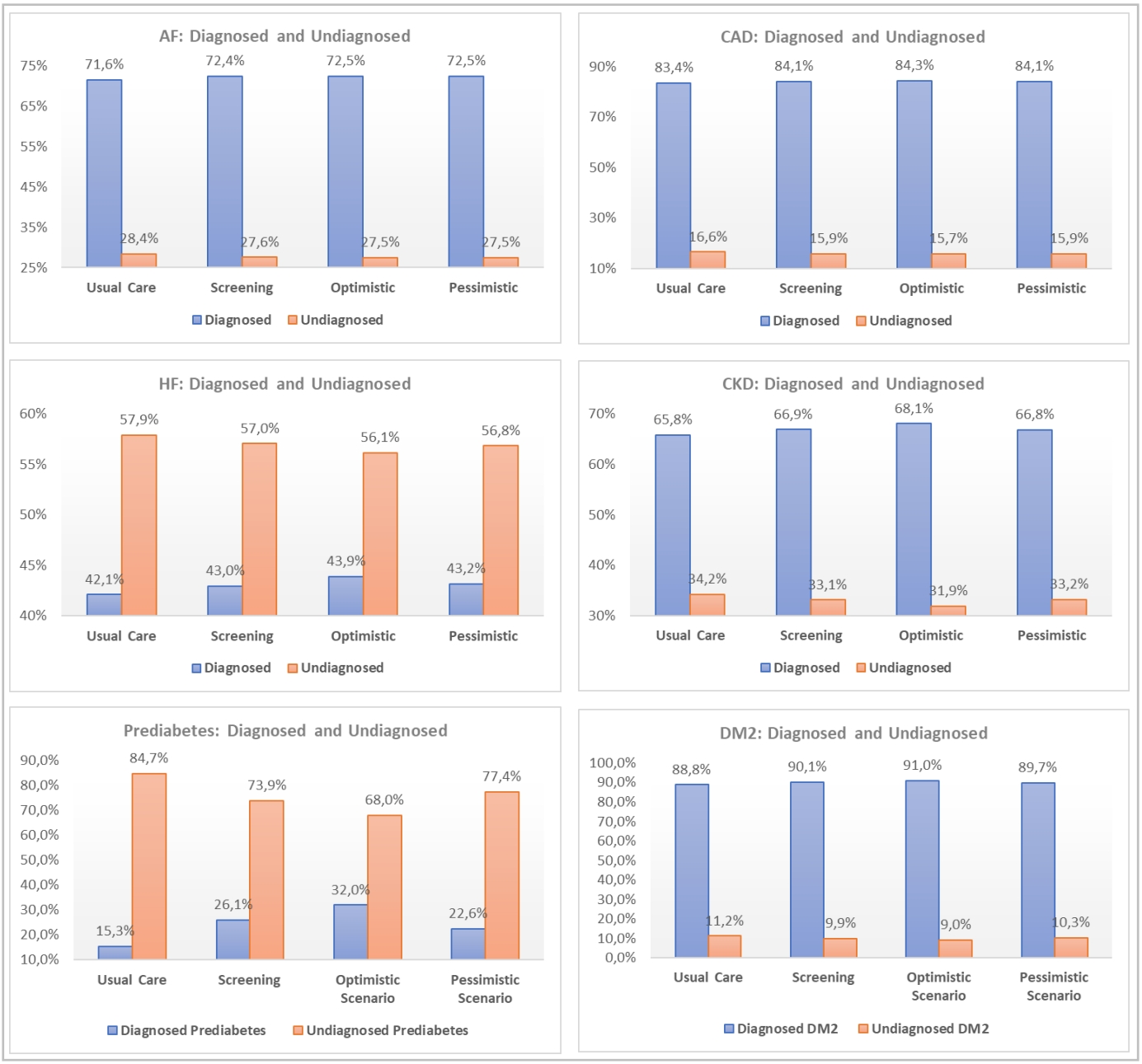



**Figure 14.** Ratio diagnosed-undiagnosed per disease domain

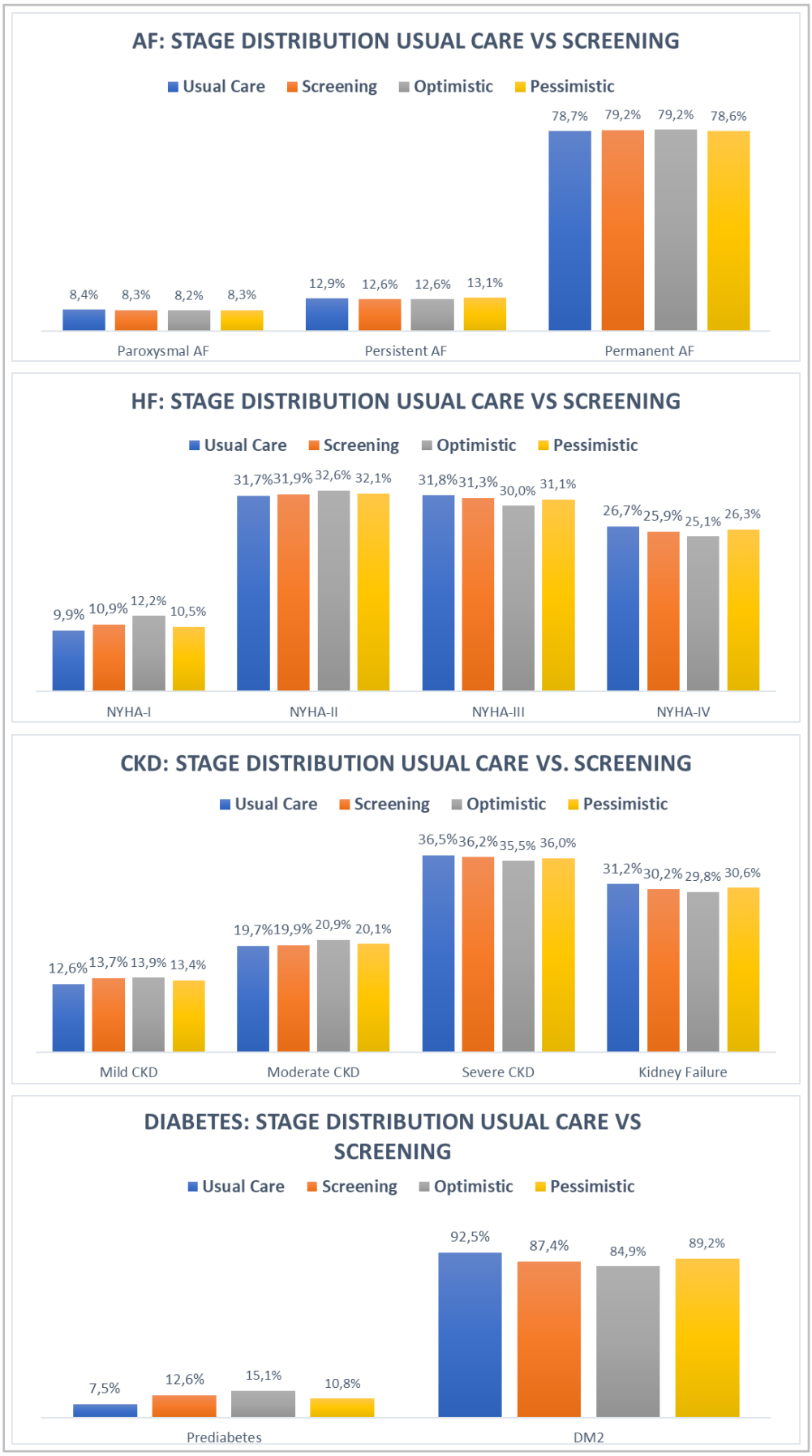



**Figure 15.** Stage distribution among the diagnosed population for usual care and screening (base-case, optimistic, and pessimistic)

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