Health Economic Evaluation of Screening for Heart Failure with NT-proBNP Compared to Clinical Assessment of Symptoms and Echocardiography Among Type 2 Diabetes Patients in A Danish Ambulatory Care Setting

- Medical Market Access -

Master thesis

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Preface

This master's thesis was produced from February to July 2024 at Medicine with Industrial Specialization, Medical Market Access, at Aalborg University under the supervision of Sabrina Storgaard Sørensen and Jan Sørensen. The thesis is produced in external collaboration with AstraZeneca and Steno Diabetes Center Copenhagen.

Originally, the master's thesis was a collaboration between group members Patrick Nasehi Jacobsen (Study number: 20193675) and Augusta Münster Spanger-Ries (Study number: 20193683). However, on May 15th 2024 the group split up. The work produced prior to the split of the group includes the preliminary development of the research question, an early draft of the background section about the clinical aspect, ideas for a literature search and a rough outline of the review section, an early draft of the decision model as well as a preliminary draft of the method section, and finally preliminary ideas for the result section.

After the group split up I have carried out the following thorough revisions of the master's thesis: The aim of the thesis has been revised and incorporated into the introduction section. The background section has thoroughly been revised and expanded with a subsection on health economic theory. The literature search has been completed, while the literature review section has been completely rewritten. The decision-analytical model has been adjusted and a few new inputs have been applied. Moreover, additional sensitivity analyses including the probabilistic sensitivity analysis, a scenario analysis, and a two-way deterministic sensitivity analysis have been produced. The majority of the method section has been rewritten. In the results section, both base case results and the results of sensitivity analyses have been revised due to changes in the model input and calculations. Finally, the abstract, introduction, discussion, conclusion, and appendix were produced after the group split.

I would like to thank my internal supervisors Sabrina Storgaard Sørensen and Jan Sørensen for educational supervision and feedback on my work. Moreover, I want to thank Bianca Kennedy Hall and Stefan Christensen from AstraZeneca, and Peter Godsk Jørgensen and Hashmat Sayed Zohori Bahrami for competent discussion and educational clinical input on the research area of type 2 diabetes, heart failure, and the Thousand&2 Cohort.

Abstract

Background: Heart failure is a common complication of type 2 diabetes mellitus, which increases mortality and risk of hospitalizations. Heart failure and type 2 diabetes mellitus impose a burden on the health and the resources used related to the treatment of these diseases, which produces a need for the prevention of heart failure among type 2 diabetes mellitus patients in the Danish healthcare sector. Current diagnostic practices in the Danish ambulatory care sector include clinical assessment of symptoms and echocardiography. However, this diagnostic practice might be insufficient in detecting the early stages of heart failure, a crucial aspect when aiming to reduce mortality and severity. Meanwhile, routine assessment of N-terminal pro-brain natriuretic peptide (NT-proBNP) levels has been suggested to detect cases of heart failure at earlier stages providing the opportunity to reduce mortality and severity of disease development.

Aim: This master thesis aims to investigate the cost-effectiveness of annual screening with N-terminal pro-brain natriuretic peptide (cut-off $\geq$400 pg/mL) compared to the current diagnostic practice of heart failure in type 2 diabetes mellitus patients in a Danish ambulatory care setting.

Methods: A cost-effectiveness analysis was performed through a Markov model comparing an annual measurement of NT-proBNP levels (cut-off $\geq$400 pg/mL) to the standard of care, including annual clinical assessment of symptoms and subsequent echocardiography. Costs and effects were assessed over a 6-year time horizon from a healthcare perspective. To assess the uncertainties of the model and inputs both deterministic and probabilistic sensitivity analyses were conducted.

Results: The base case results indicate that screening with NT-proBNP with a cut-off of $\geq$400 pg/mL is cost-effective compared to standard of care with an ICER of -31.350 DKK/QALY. The base case results indicate that the NT-proBNP strategy was associated with lower costs and greater effects than the standard of care. Deterministic sensitivity analysis results show that changes in NT-proBNP cut-off value and mean age for entering the model impact the results. However, probabilistic sensitivity analysis results indicate a high probability of the NT-proBNP strategy being cost-effective compared to the standard of care when applying an internationally established willingness-to-pay threshold.

Conclusion: Based on the best available data, the assumptions made in the analysis, and the cost-effectiveness at a willingness-to-pay threshold of 260.000 DKK/QALY, this study supports the implementation of an annual NT-proBNP screening for heart failure among type 2 diabetes mellitus patients in Danish ambulatory care centers.

Abbreviations

ACE	Angiotensin-converting enzyme
CBA	Cost-benefit analysis
CEA	Cost-effectiveness analysis
CfD	Center for Diabetes Research
CUA	Cost-utility analysis
BNP	Brain natriuretic peptide
CEAC	Cost-effectiveness acceptability curve
CfD	Center for Diabetes Research
CI	Confidence interval
CPI	Consumer price index
CVD	Cardiovascular disease
DCS	Danish Society of Cardiology
DES	Danish Endocrine Society
DKK	Danish Kroner
DM	Diabetes mellitus
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
ECG	Electrocardiogram
EF	Ejection fraction
EQ-5D-3L	EuroQol Group 5-Dimension 3-Level Self-Report Questionnaire
ESC	European Society of Cardiology
GLP-1	Glucagon-like peptide 1
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HHF	Hospitalization for HF
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICD-10	International Classification of Diseases, Tenth Revision
ICE	Incremental cost-effectiveness
ICER	Incremental cost-effectiveness ratio
LVEF	Left ventricular ejection fraction

LY	Life year
mL	milliliter
NICE	National Institute for Health and Clinical Excellence
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OR	Odds ratio
pg	picogram
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SDC	Steno Diabetes Center
SE	Standard error
SF-12	12-Item Short Form Survey
SGLT2i	Sodium-glucose co-transporter 2 inhibitor
SoC	Standard of care
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TP	Transition probability
UK	United Kingdom
USA	United States of America
WTP	Willingness to pay

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1. Introduction

Heart failure (HF) is a cardiovascular disease (CVD) associated with poor prognosis, including increased risk of hospital admission and mortality. The risk of HF is increased by type 2 diabetes mellitus (T2DM) and HF is a serious and common cardiovascular complication of T2DM [1, 2]. In fact, the incidence of HF is more than twice as high among patients with DM compared to patients without DM [2]. Moreover, patients with T2DM have a 33% higher risk of hospitalization due to HF (HHF) compared to patients without T2DM [1]. While diabetes mellitus (DM) imposes a considerable economic burden on the Danish healthcare sector and society, most of these costs are associated with DM patients with major complications, such as HF. When looking at the healthcare costs associated with DM, the majority is attributed to the secondary healthcare sector which includes both ambulatory care and hospital admissions [3]. T2DM patients in Danish ambulatory care are characterized by inadequately controlled glycaemic levels, which is a crucial risk factor to control when preventing cardiovascular complications [1, 4]. Although early diagnosis is crucial due to the high mortality and resource consumption related to HF and T2DM, clinical assessment and subsequent echocardiography are the predominant diagnosis methods of HF in Danish ambulatory care [5]. However, natriuretic peptides, such as N-terminal pro-brain natriuretic peptide (NT-proBNP), are indicated to possess predictive and diagnostic value of HF among T2DM patients [6–9]. Thus, NT-proBNP could prove useful as a screening biomarker, detecting HF among T2DM patients, with no or indistinct symptoms of HF [1]. While international guidelines recommend routine assessment of NT-proBNP, the biomarker is not recommended as a screening tool in Danish healthcare [10, 11]. The Thousand&2 Cohort is a Danish cohort consisting of T2DM patients in ambulatory care and the data has previously been utilized to investigate NT-proBNP as a risk marker of CVD among T2DM patients [8]. The cohort possesses features related to T2DM, CVD, hospitalizations, and mortality, and is thus both informing and representative of the health and economic burden among T2DM patients at risk of and suffering from HF [4].

This master thesis thus aims to simulate the use of NT-proBNP ($\geq$400 pg/mL) as a screening marker for HF in the Thousand&2 Cohort through decision analytical modeling and investigate the cost-effectiveness of annual NT-proBNP screening compared to the current standard of care (SoC) in a T2DM population in a Danish ambulatory care setting. In this health economic evaluation, the current diagnostic practice includes clinical assessment of symptoms and subsequent echocardiography in case of symptoms. The cost-effectiveness will be estimated through a Markov model simulating a cohort of 1000 patients and the patient pathway of T2DM patients developing HF. Data from the literature will form the basis of the current diagnostic practice of HF in Danish ambulatory care and dis-

criminatory values of NT-proBNP in this specific population. The impact on the cost-effectiveness of the uncertainty related to each parameter will be examined through a one-way deterministic sensitivity analysis and a probabilistic sensitivity analysis. The impact of diagnostic accuracy of NT-proBNP at different cut-off values and mean age in the population will be examined through individual scenario analyses and two-way deterministic sensitivity analysis.

2. Clinical Background and Health Economic Theory

This section will cover the pathophysiology and diagnostic guidelines of heart failure (HF) among type 2 diabetes mellitus (T2DM) patients. The section will also explain the principles of screening, diagnostic accuracy, and how health economic evaluation can provide input for decision-makers in the process of optimizing healthcare through new interventions.

2.1 Type 2 Diabetes Mellitus and Risk of Heart Failure

2.1.1 Type 2 Diabetes Mellitus

Diabetes mellitus (DM) is an endocrine disease caused by insufficient insulin secretion in proportion to the insulin sensitivity of the tissue. T2DM is the most common type of DM and is caused by insulin resistance rather than decreased insulin secretion which is the cause of type 1 diabetes mellitus (T1DM) [12, 13]. Insulin resistance causes increased blood glucose levels, subsequently leading to dyslipidemia and long-term complications including macroangiopathy, retinopathy, nephropathy, and neuropathy among others [14]. The proportion of people with T2DM in Denmark has increased significantly from 2015 to 2023 with no indication of slowing down. Most recently, a report published by the Danish Diabetes Association in 2023 estimated that at least 356,000 people in Denmark are living with T2DM. Meanwhile, Steno Diabetes Center (SDC) estimated that approximately 100.000 people in Denmark in 2011 were living with undiagnosed T2DM [15].

Currently, about 88% of the estimated 322,000 individuals in Denmark diagnosed with T2DM undergo treatment in the primary healthcare sector. The remaining 12% seek are treated in the secondary healthcare sector at specialized centers such as SDC or diabetes outpatient clinics, primarily due to progressing T2DM requiring insulin treatment or complications necessitating specialized attention. The primary objective in managing T2DM, following the Danish guidelines, is to achieve stable and low long-term blood sugar levels no matter the specific treatment site [15]. This is crucial due to the fact that people with T2DM face an increased mortality risk compared to people of similar age and sex without T2DM. In particular, cardiovascular disease (CVD) affects approximately one-third of all people with T2DM and accounts for half of all deaths in this population despite major advances in the treatment of the disease [16]. The heightened risk of CVD among individuals with T2DM is widely acknowledged. As such, various factors, including HbA1c levels, blood pressure, lipid profiles, and kidney function markers, have been proposed as indicators for risk assessment, aiding in the timely

identification of T2DM patients at increased risk of CVD [17].

2.1.2 Heart Failure and Risk Factors

CVD is one of the most common complications and causes of death associated with T2DM. While ischemic heart disease and stroke are widely recognized cardiovascular complications, HF emerges as a significant and equally frequent complication. HF commonly stems from acute myocardial infarction and hypertension, yet research indicates that T2DM independently increases the risk of HF [18]. HF is a clinical condition marked by common symptoms like fatigue, shortness of breath, and edema, alongside changes in myocardial function identified through imaging techniques, typically echocardiography [1]. The HF condition is categorized into two types: heart failure with reduced ejection fraction (HFrEF) with EF<40%, and heart failure with preserved EF (HFpEF) with EF>50% [1]. The prognosis is unfavorable for patients suffering from both T2DM and HF. Patients with T2DM are admitted for exacerbations of HF more than twice as often as those without T2DM, and the risk of mortality is doubled [2]. The treatment and management of HF entails addressing overall cardiovascular risks through controlling blood pressure and dyslipidemia, promoting weight loss, and supporting smoking cessation. Additionally, maintaining optimal glycemic control is crucial in preventing cardiovascular complications [1].

2.1.3 Economic Burden of Type 2 Diabetes Mellitus and Heart Failure

DM is a highly prevalent chronic disease in Denmark with a high risk of complications requiring treatment in both the primary and secondary healthcare sectors [15]. Consequently, DM imposes an economic burden on Danish society. For example, Sortsø et al. (2016) found that societal costs associated with DM patients amount to almost 40 billion where the majority of expenses are attributed to productivity loss. Such losses amount to over 13 billion DKK, followed by approximately 12 billion DKK for the healthcare sector, according to Sortsø et al. (2016). Concerning healthcare costs, the majority is attributed to the secondary healthcare sector, and only a minor proportion is attributed to the primary care sector [3]. As one of the only and largest studies to date, Sortsø et al. (2016), provide insights into the correlation between the expenses incurred by patients with DM, both with and without complications, in contrast to those without DM, using data extracted from national registries [3]. The study used a novel approach of categorizing patients based on the progression of complications, into no, minor, and major complications, in which HF is considered a major complication, and found that the majority of expenses are accrued by DM patients with major complications when considering the total healthcare costs per person-year [3].

2.2 Diagnosing Heart Failure in Type 2 Diabetes Patients

For T2DM patients treated at ambulatory care centers guidelines recommend routine assessments every 3-4 months and an annual more comprehensive assessment and examination of possible com-

plications. The annual check-up at the ambulatory care center includes an examination of symptoms and clinical signs of CVD and screening for cardiovascular risk factors such as cholesterol [19]. The 2023 European Society of Cardiology (ESC) guidelines recommend the following diagnostic tests when HF is suspected: I) Measurement of natriuretic peptides, if available, with specific cut-off values suggesting the likelihood of HF diagnosis, II) Electrocardiogram (ECG) to detect abnormalities II) Echocardiography to assess cardiac function IV) Chest X-ray to investigate other causes of dyspnea V) Routine blood tests to differentiate HF from other conditions and guide therapy, VI) Additional diagnostic tests may be considered based on specific suspicions. Regular evaluation for HF symptoms and signs is recommended in T2DM patients, including systematic surveys for symptoms like breathlessness and signs like weight gain or peripheral edema. This ongoing monitoring helps detect the transition from being at risk of HF to developing the condition [20].

2.2.1 Echocardiography

Echocardiography is the predominant imaging method utilized in the detection and ongoing monitoring of CVDs due to its advantages in diagnosis, management, and post-treatment monitoring. For individuals with HF, echocardiography offers crucial insights into disease severity, aids in treatment strategy decisions, predicts prognosis, and evaluates treatment responses. Recognizing and treating HF in patients with T2DM is essential for clinicians, as timely detection of HF can greatly decrease the risk of future adverse cardiovascular events. Echocardiography serves as a fundamental imaging technique in diagnosing HF, particularly in cases presenting typical symptoms and elevated levels of natriuretic peptides [21]. The Danish Society of Cardiology (DCS) guidelines recommend that all T2DM patients who exhibit clinical signs suggestive of HF should undergo echocardiography, especially when these signs are accompanied by high-risk clinical markers such as risk profile, symptomatology, and/or abnormal ECG results. The high-risk markers are defined as cardiac dysfunction within medical history, clinical, ECG abnormalities, and imaging [5]. While guidelines recommend direct referral for cardiac assessment (including echocardiography) in case of clinical signs of HF and high-risk markers, there are cases of absence of high-risk markers, yet with sustained suspicion of HF. In these situations, measurement of natriuretic peptides may prove useful in effectively ruling out HF [19].

2.2.2 Natriuretic Peptides

When diagnosing or assessing symptoms indicating HF in the primary healthcare sector and emergency department in the secondary sector the DCS recommends the utilization of natriuretic peptides. Specifically, brain natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are recommended by DCS when assessing patients with suspected HF without high-risk markers of cardiac dysfunction [5]. BNP is synthesized mainly in the left ventricle induced by an overload of pressure and expansion of the ventricle. Cardiac stress results in rapid synthesis and secretion of the prehormone, proBNP,

from the myocytes into surrounding tissue that is subsequently split into the active BNP and inactive NT-proBNP both of which can be detected in plasma [1, 22]. While BNP is actively cleared from plasma, NT-proBNP is passively cleared through renal excretion resulting in the half-life of BNP being approximately 6 times higher than that of NT-proBNP leading to lower plasma concentrations of BNP compared to NT-proBNP [23]. Consequently, NT-proBNP is more stable over time and might constitute a better diagnostic biomarker in patients with suspected HF than BNP [22, 24].

2.2.2.1 NT-proBNP and Current Guidelines

HF can lead to elevated levels of NT-proBNP and the biomarker is recommended by DCS guidelines in the diagnosis of suspected HF in primary care [5, 20, 22]. The DCS position paper on BNP in HF proposes different NT-proBNP concentrations used in primary care, indicating low or high risk of HF. In Danish primary care practice, NT-proBNP is used as a rule-out test for HF, at a threshold value of $\leq$125 pg/mL in patients aged <75 years. The DCS position paper describes that the threshold value of $\leq$125 pg/mL has a high sensitivity and low specificity for HF, which results in a high number of false positive results [5]. A Danish systematic review from 2018 found that the threshold value of $\leq$125 pg/mL has a sensitivity ranging from 0,88 to 1, while the specificity ranges from 0,49 to 0,89 [25]. The DCS guidelines propose a threshold of $\geq$450 pg/mL for patients aged <50 years at high risk of HF, and a threshold of $\leq$900 pg/mL in patients aged 50-74 years at high risk of HF. An NT-proBNP concentration of $\leq$125 pg/mL indicates a low probability of HF and the diagnosis can presumably be ruled out. Meanwhile, a concentration of $\geq$450 pg/mL indicates a high risk of HF and patients should consequently be referred for an echocardiography [5]. These recommendations are applicable for patients suspected of HF regardless of T2DM as DCS treatment guidelines for diabetes and cardiovascular disease refer to the DCS position paper regarding BNP in HF [5, 19].

In T2DM ambulatory care, NT-proBNP is also recommended as a rule-out biomarker for HF, while echocardiography confirms the diagnosis [19]. However, studies show that in addition to the rule-out of HF, NT-proBNP has a predictive value for identifying T2DM patients at risk for developing HF [7–9]. However, NT-proBNP is not implemented at the annual check-ups in the Danish ambulatory care centers for T2DM patients. This stands in contrast to the recommendations put forward in a report on the universal definition and classification of HF by the Heart Failure Society of America, Heart Failure Association of the ESC, Japanese Heart Failure Society, and Writing Committee of the Universal Definition of Heart Failure that suggest routine assessment of NT-proBNP and BNP values in T2DM patients without current or prior symptoms or clinical signs of HF. For patients in ambulatory care, the report recommends a cut-off value of NT-proBNP $\geq$125 pg/mL as a rule-out value of HF [10]. Although NT-proBNP is implemented as a rule-out biomarker in the primary care sector and emergency departments for the general population in Denmark, it is not utilized in ambulatory care

[5]. T2DM patients are at higher risk of developing HF and early detection of the condition is thus crucial, due to high mortality and resource consumption related to T2DM and its' complications [2, 3]. While echocardiography remains the predominant imaging method for HF, the procedure requires referral depending on clinical signs and high-risk markers of HF [11, 21]. Danish guidelines do not recommend NT-proBNP in screening for HF however, international guidelines recommend routine assessment of NT-proBNP among T2DM patients without current or previous symptoms of HF while studies indicate that biomarkers such as NT-proBNP can be useful in the early detection of HF in T2DM patients [1, 10, 11]. This inconsistency in Danish and international guidelines on the use of NT-proBNP in T2DM patients presumably causes a difference in the resource use and health related to the detection of HF among T2DM patients in Denmark and internationally. Consequently, this raises questions on how resources should be allocated to optimize the health among T2DM patients.

2.3 Health Economic Evaluation

The resources within the healthcare sector are limited and implementing new health technology or interventions at a certain cost will subsequently lead to removing these resources from elsewhere within the healthcare sector. Consequently, healthcare decision-making should be based on systematic analyses informing decision-makers on the benefits and consequences of certain options [26]. Health economic evaluation therefore requires a comparison of at least two alternative healthcare interventions in which both costs and health benefits related to each alternative are evaluated [26].

There are different types of full health economic evaluation, differentiated by the valuation of the effect of the interventions. Common for all full health economic evaluations are costs that are measured in monetary units. However, in a cost-effectiveness analysis (CEA) the effect is measured in natural units which include a variety of clinical endpoints [26, 27]. For T2DM and HF patients these could include glycaemic levels, hospitalizations due to HF (HHF) averted, and life-years (LY) gained among others. CEA is different from the cost-utility analysis (CUA) which includes quality-adjusted life year (QALY) as a health outcome. QALY is based on the life expectancy and utility of the patient. The utility score is a reflection of quality of life and measures the preference for being in a particular health state [27]. The effect of the cost-benefit analysis (CBA) is expressed as monetary units with the aim of judging healthcare decisions like other public choices. When applying the perspective on healthcare that the aim is to improve overall welfare it is an advantage for the effect to be expressed in monetary units to inform decisions across public and private sectors. However, the CBA requires a conversion of health outcomes to monetary units based on patient preferences [26, 27]. When comparing the CEA and CUA they both aim to maximize the societal health benefit, but both methods impose advantages as well as disadvantages. As the CEA applies natural units as health outcomes it often requires fewer resources to collect these since these are already measured in clinical effectiveness studies. Moreover, these clinical endpoints are known to clinicians and are thus easier

for them to interpret. However, the use of natural units imposes a challenge when determining the most appropriate outcome and complicates comparisons between different diseases. Differently, the CUA allows for comparison across diseases, interventions, and populations, due to the broad health outcome QALY [27].

In both CEAs and CUAs the comparison of two or more alternative healthcare interventions measures the incremental costs and effects between the alternatives. By comparing the incremental costs and effects the question of additional value for money is addressed. In CEAs and CUAs this comparison is expressed as the incremental cost-effectiveness ratio (ICER). The ICER is calculated by the formula:

$$ICER = \frac{Cost_B - Cost_A}{Effect_B - Effect_A} \tag{2.1}$$

In formula 2.1 $Cost_A$ represents the expected costs associated with alternative A, the current practice, while $Cost_B$ represents the expected cost associated with alternative B, the new intervention. Likewise, $Effect_A$ and $Effect_B$ represent the expected health outcome associated with the current and new interventions, respectively. As a low ICER implies more value for money compared to a higher ICER, policymakers wish to implement healthcare interventions with an ICER as low as possible. To determine if one intervention is cost-effective compared to another it is necessary to establish a willingness-to-pay (WTP) threshold, which represents the maximum ICER that policymakers will accept [26, 27]. Estimating the expected value and cost-effectiveness related to healthcare interventions requires a framework and defined approach for data collection. Previously, health economic evaluations have been primarily based on single clinical studies, but in recent years decision-analytical modeling has become more widespread within health economics [26].

2.3.1 Decision-analytical Modeling

Decision-analytical modeling is a systematic approach that provides a structured framework to support decision-making under uncertainty by identifying the most cost-effective option. Decision-analytical modeling aims to evaluate specific clinical pathways and decisions while incorporating and drawing on evidence from a wide range of sources. Thus, decision-analytical models can include evidence from randomized clinical trials, surveys, cohort studies, etc [26]. Several model types can be applied, but the most common within health economic evaluation are the Markov models and decision trees. Both modeling approaches have limitations.

The decision tree model entails identifying the expected value (costs and effects) of different healthcare alternatives (branches) by structuring each branch and assigning probabilities to the patient path-

way illustrated in the decision tree. While the decision tree model is more suitable for modeling pathways including few health states with a short time horizon, time is not an included aspect unless explicitly incorporated into the different health states or branches of the decision tree. Moreover, a decision-tree model that includes long-term disease courses will eventually contain multiple branches and therefore become highly complex. The lack of a temporal aspect alongside the complexity related to modeling multiple branches makes the decision tree model unsuitable for chronic diseases such as T2DM or recurrent episodes such as HHF during a lifetime [26, 27]. Differently the Markov model is more suitable when modeling chronic diseases as it is based on several health states in which patients can transition between. Moreover, the Markov model includes a temporal aspect by evaluating the costs and effects of patients over discrete time periods. These discrete time periods are called cycles and define the time in which a patient can occupy the health states of the model. Each health state is associated with costs and effects, while transition probabilities determine how patients transition between health states over time. The Markov model hereby allows for modeling over a long period of time with patients moving between health states multiple times which is essential when modeling chronic diseases such as T2DM and HF [26].

2.3.2 Evaluation of Screening Programs

Early detection of HF among T2DM patients is crucial due to the poor prognosis associated with the condition [1, 11]. Early detection of disease falls under the term 'medical screening' which aims to reduce morbidity and mortality through early detection and intervention [28, 29]. Screening can fall under both primary and secondary prevention of disease, in which primary prevention entails identifying individuals at risk of disease while secondary prevention entails detecting disease in an early and asymptomatic stage [28]. NT-proBNP has been indicated to possess both predictive and diagnostic abilities. However, there is more evidence on the diagnostic accuracy of NT-proBNP, and the biomarker is currently only utilized in the primary healthcare sector as a diagnostic rule-out biomarker for HF in Denmark [1, 5, 8].

To support policymakers in the decision to implement routine assessment of NT-proBNP among T2DM patients, a health economic evaluation of a screening program including NT-proBNP is crucial. Aside from the costs and effects of different screening and diagnostic strategies, it is important to consider the validity of the diagnostic tests when conducting health economic evaluations of screening programs [29]. The validity, or diagnostic accuracy, is dependent on the sensitivity, specificity, and predictive values of the diagnostic test. Sensitivity represents the probability that a test will detect disease in a person who is sick (true positive) while specificity is the probability that the test will tell a healthy person that they are healthy (true negative). The sensitivity and specificity hereby represent the ability of a test to discriminate between disease and health [30]. These are different from the predictive values, negative predictive value (NPV), and positive predictive value (PPV), which

represent the ability of a test to identify patients at risk of developing disease. While PPV and NPV are dependent on the prevalence of the disease in the population under investigation, sensitivity, and specificity are not and can therefore be transferred from one setting to another [30].

When evaluating diagnostic tools such as NT-proBNP, a certain diagnostic cut-off value is necessary to distinguish between disease and health. Hereby the sensitivity and specificity are a function of the cut-off value and vary when changing the cut-off value [29]. Another important aspect to consider when evaluating screening programs is the consequences related to the diagnostic accuracy of the test under investigation. As sensitivity and specificity can never be 100% for a single diagnostic test some false positive or false negative test results will inevitably occur [28]. Consequently, there will be some unnecessary resource consumption related to false positive results and increased morbidity and mortality related to an increase in false negative results. Hereby, determining the value of a diagnostic test will require consideration of both clinical costs and mortality and morbidity [28, 31].

When evaluating diagnostics or screening programs both final and intermediate outcomes are relevant. While final outcomes include endpoints such as LYs gained or QALYs gained, intermediate outcomes include HHFs averted or HF cases detected. While the intermediate outcomes reflect the ability to diagnose disease or reduce the development of severity they should however be interpreted with caution. It is important to be aware that even though a new diagnostic test identifies more cases, they might be less serious, but still expensive to treat. Therefore it is important to apply final outcomes such as LYs and QALY when assessing the cost-effectiveness [26].

2.3.3 Sensitivity Analysis

The estimation of cost-effectiveness will always entail uncertainty due to the evidence related to healthcare interventions. It is, therefore, necessary to consider this uncertainty when conducting health economic evaluations as this will not only support policymakers in justifying the implementation of new health interventions but also identify what further evidence may be required to make certain decisions [26]. Sensitivity analyses are conducted to systematically investigate the uncertainty related to assumptions made in the structure and input of the health economic evaluation and the impact of this uncertainty on the results. There are different types of uncertainty worth investigating, including parameter uncertainty, structural uncertainty, and methodological uncertainty. Parameter uncertainty refers to the uncertainty related to the estimates of the input of the model, while structural uncertainty refers to the structure of a decision-analytical model. Meanwhile, methodological uncertainty refers to the assumptions related to the methods applied in the health economic evaluation. To investigate these uncertainties different types of sensitivity analyses can be conducted including deterministic and probabilistic sensitivity analyses [26].

2.3.3.1 Deterministic Sensitivity Analysis

The deterministic sensitivity analysis (DSA) is based on point estimates and the results of the DSA are hereby not influenced by randomness. The most simple form of a DSA is the one-way sensitivity analysis. Here, each parameter is explored reporting the cost-effectiveness results of the lower and upper bounds of each parameter. This makes it possible to determine how sensitive the model is to the uncertainty related to the individual parameters. Such an analysis does however not allow for investigation of combined uncertainty [26, 32]. To (partly) investigate the combined uncertainty of more than one parameter a two-way sensitivity analysis can be conducted. When conducting a two-way sensitivity analysis, two parameters are changed simultaneously [26]. Another common type of DSA is scenario analyses which are relevant when more estimates for the same parameter are available [32]. This could be relevant when investigating diagnostic tools at different cut-off values for which every cut-off value provides a new set of sensitivity and specificity values [30, 31]. The DSAs are however all limited as they do not consider the probability related to the parameters and hereby do not inform on the decision uncertainty [32].

2.3.3.2 Probabilistic Sensitivity Analysis

The probabilistic sensitivity analysis (PSA) is a stochastic sensitivity analysis in which the parameters of the model are based on distributions. Each parameter will be assigned a type of distribution based on its characteristics. For example, the transition probabilities and utility could be assigned a β distribution as this probability is restricted to $0 \leq x \geq 1$. Meanwhile, the γ distribution is restricted to $0 \leq x \geq \infty$ and is characterized by being right-skewed. These characteristics are typically applicable for the distribution of real-life costs and the γ distribution is therefore evident as a distribution applied for costs [26, 32]. Other distributions include log-normal distributions which are applicable for disutility and ratios, and normal distributions which are applicable for any parameter. It is, however, important to note that a sufficient sample size is required to assume a normal distribution which is often a challenge [26]. The PSA is based on the second-order Monte Carlo simulation in which the model inputs are drawn from the respective parameter distributions calculating the ICER of this particular set of parameters. Sampling the inputs and recording the respective outputs is repeated multiple times producing i.e. 10.000 iterations [26, 32]. The results of the PSA are commonly illustrated in incremental cost-effectiveness (ICE) scatterplots in which each estimate of the ICER is plotted illustrating the distribution of results. Moreover, the PSA can provide information on the probability that a new intervention will be cost-effective compared to a comparator at a given WTP threshold. These results are typically presented in a cost-effectiveness acceptability curve (CEAC) which is a quantification of the ICE scatterplot. The CEAC illustrates the probability that each of the healthcare interventions will be cost-effective at any given WTP threshold [26]. The PSA is therefore a sensitivity analysis that investigates the parameter uncertainty and represents the decision uncertainty [26, 32].

2.4 Summary

HF among T2DM patients is a frequent and critical complication requiring early diagnosis and treatment to reduce morbidity and mortality [1, 18]. Studies indicate that NT-proBNP possesses diagnostic abilities useful among T2DM patients, however, Danish and international guidelines differ in recommendations on the use of NT-proBNP versus echocardiography and clinical assessment [1, 10, 25]. When comparing these diagnostic approaches it is necessary to consider both health outcomes and resource consumption related to each strategy, through health economic evaluations [26]. Based on the clinical aspects of HF among T2DM patients, guidelines on the use of NT-proBNP as a screening tool, and the health economic questions raised in this section it is necessary to investigate how this issue has been addressed through health economic research, to assess the health and economic implications related to NT-proBNP as a screening tool in T2DM patients.

3. Current Research

To explore studies and research on the cost-effectiveness of NT-proBNP in patients with HF I conducted a systematic literature search and a concise review, which is presented in the following.

3.1 Literature Search

To identify the current research on the cost-effectiveness of NT-proBNP diagnosis and screening in HF patients a systematic literature search was conducted in PubMed. The Population, Intervention, Comparison, Outcome (PICO) model was applied to identify relevant search terms. The Comparison aspect of the PICO model was excluded to ensure a broad search including all relevant research (table 3.1). The search string contained both specific Mesh-terms and free-text terms.

Table 3.1: *Systematic literature search: Current research*

P	I	C	O
Heart failure patients	NT-proBNP		Health economic evaluation
Systolic heart failure	BNP		Cost-effectiveness analysis
Diastolic heart failure	Natriuretic peptide		Cost-utility analysis

The literature search in PubMed resulted in a total of 146 hits (153 including duplicates). These studies were screened by title, abstract, full-text reading, as illustrated in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart in figure 3.1. The assessment of full-text articles was based on the inclusion and exclusion criteria listed in table 3.2. The screening resulted in inclusion of 10 studies examining the cost-effectiveness or cost-utility of employing NT-proBNP or BNP in screening, diagnosing, and risk assessment of patients with various types of HF.

Table 3.2: *Inclusion and exclusion criteria*

Inclusion criteria	Exclusion criteria
Health Economic evaluation	Editorials
Elderly population	Case reports
Model based cost-effectiveness analysis or cost-utility analysis	Acute dyspnea
Health technology assessment	Device therapy
Decision modelling	Treatment guidelines
Naturetic peptides	
NT-proBNP	
Heart failure	

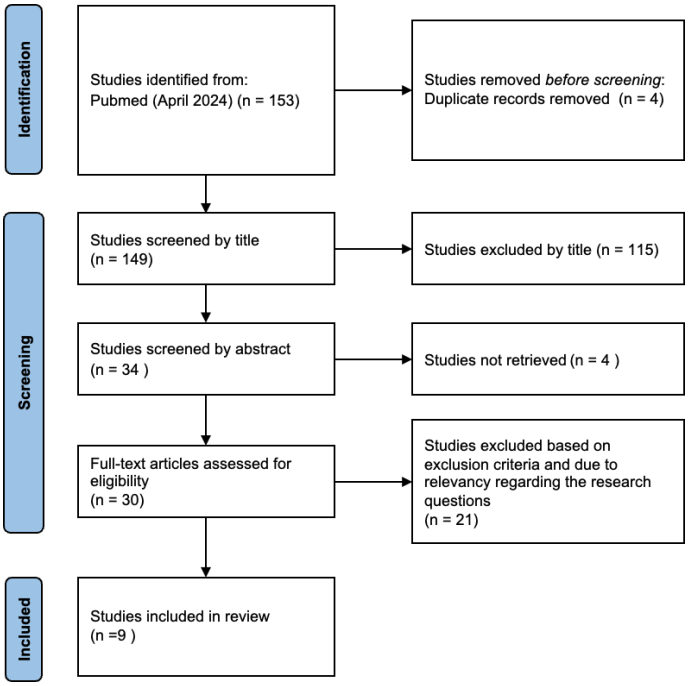

Figure 3.1: *PRISMA-flowchart visualizing the identification, screening, and number of included studies in the literature review*

3.2 Literature Review

This review includes the ten studies published between 2004 to 2023 identified in the systematic literature search and presents and compares different methodological aspects of the studies. The characteristics of the included studies are presented in table 3.3.

3.2.1 Population

The studies included in this review investigated a variety of populations in different healthcare settings. Four studies did not specify the age of the population [33–36] however, one of the studies is a systematic review and thus includes several studies with varying populations [35]. Two studies compared populations of ages <75 years and $\geq$75 years [37, 38], while one study investigated a population aged 35-85 years [39]. Another study investigated a population aged >60 years [40], and the last study investigated a hypothetical cohort of men and women aged 60 years [41]. The studies included in this review thus vary in the age of populations investigated, while several studies include populations with broad age groups.

When looking at the healthcare setting, three studies investigate the use of natriuretic peptides in emergency departments (ED) [33, 34, 42] while two studies investigates the use of natriuretic peptides specifically in outpatient/ambulatory care [36, 39]. Another important aspect is the inclusion of T2DM patients in the study populations. Only one of ten studies investigated screening with NT-proBNP in T2DM patients [40], while the remaining studies focused on acute HF [33, 34, 42], patients

with HF [35, 37], or patients discharged from HHF [36, 38, 39].

Table 3.3: *Articles overview*

Author (year)	Population and setting	Countries	Intervention vs comparator	Model type	Time horizon, perspective	Outcomes
Walkley et al. (2023)	Patients in EDs with suspected acute HF	UK	RI/RO NT-proBNP strategy vs RO NT-proBNP strategy vs clinical decision alone	Hybrid decision tree/ semi-Markov model	Lifetime horizon, healthcare payer perspective	Costs and QALY
Walter et al. (2023)	Patients ≥60 years with/without T2DM	Austria, Switzerland	HF screening using NT-proBNP vs no screening	Time-discrete Markov model	Lifetime horizon, healthcare system perspective	Costs, QALY and LY
Siebert et al. (2021)	Patients suspected of acute HF in ED	USA	NT-proBNP driven diagnosis vs diagnosis without NT-proBNP	Decision-tree model	6-months time horizon, US medicare perspective	SAEs
Pufulete (2017)	Patients with HF in primary and secondary care	UK	BNP-guided strategy vs standard guided strategy	Markov model	Lifetime horizon, UK NHS perspective	Costs and QALY
Jafari et al. (2018)	Patients with HF	USA, UK, Canada, Switzerland	NT-proBNP-/BNP-guided care vs usual care	Majority of studies used Markov models, one used decision tree model	Most studies used lifetime horizon, one used 20-year time horizon	Majority of studies used QALY
Mohiuddin et al. (2016)	Recently hospitalized patients with HF	UK	Specialist-led BNP-guided care vs specialist-led clinically guided care	Markov model	Lifetime horizon	Costs and QALY
Morimoto et al. (2004)	Patients in outpatient care after hospitalization due to HF with LVEF 40%	Japan	BNP measurement every 3 months vs no BNP measurement	Markov model	9 months	Cost and QALY
Moertl et al. (2012)	Patients discharged from HHF into primary, home, or ambulatory care	Austria Canada	Usual care vs multidisciplinary care vs NT-proBNP guided intensive care	Markov model	20-year time horizon, payer perspective	Long-term costs and health outcomes
Heidenreich et al. (2004)	Patients (60 years old)	USA	BNP and echo vs BNP only vs echo only vs no screening	Decision model	Lifetime horizon, societal perspective	Costs and QALY
Siebert et al. (2006)	Dyspneic patients (21 years old) presenting to ED	USA	Standard clinical assessment vs NT-proBNP guided evaluation	Decision analytic model	60 days time horizon	SAEs and direct medical costs

Abbreviations: BNP, brain natriuretic peptide; ED, emergency department; HF; heart failure; HHF, hospitalization due to HF; LVEF, left ventricular ejection fraction; LY, life year; NHS, National Health Service; NT-proBNP, N-terminal pro-brain natriuretic peptide; QALY, quality-adjusted life year; RI, rule-in; RO, rule-out; SAE, severe adverse event; T2DM, type 2 diabetes mellitus

3.2.2 Intervention and Comparator

Interventions and comparators included a variety of screening strategies and natriuretic peptide-guided treatment strategies. Six studies included NT-proBNP assessment [7, 33, 34, 36, 40, 42] while the remaining four studies included BNP assessment [37–39, 41]. Only one study investigated an NT-proBNP strategy for HF [40] while the majority of the remaining studies investigated assessment of NT-proBNP or BNP as guidance on treatment for HF [35–38, 42]. However, one study did investigate screening for HF with BNP [41].

When looking at comparators in the different studies, they included primarily no screening [40, 41], diagnosis without NT-proBNP [33, 34], or usual/standard care [34–38]. The comparator assessment strategies primarily included clinical assessment of symptoms and subsequent echocardiography [40], echocardiography for all patients [41], or clinical assessment alone [33]. However, in many studies, the definition and contents of the comparator strategies were unclear [34, 36–39, 42].

3.2.3 Model type

In terms of model types, the studies included decision-tree models and Markov models, but also one hybrid model [33]. Five studies reported the use of a Markov model [36–40] which is supported by the findings from the literature review by Jafari et al. (2018). The review by Jafari et al. (2018) found that the majority of studies investigating the cost-effectiveness of natriuretic peptide-guided care utilized Markov models [35]. Moreover, the findings relating to decision-tree models reported by Jafari et al. (2018) are also consistent with this review in which only one study applied a decision-tree model [34, 35]. Meanwhile, one study applied a hybrid decision-tree/semi-Markov model [33] and two studies reported utilizing decision (analytical) models [41, 42]. In the five studies applying Markov models, the cycle length is either 1 month [36] 3 months [37–40]. Furthermore, among the studies applying Markov models, one study bases the definition of health states on the New York Heart Association (NYHA) stages ranging from I to IV [40] while another study based the health states on the progression of HF in which the number of HHF was used as a proxy for HF disease progression [36]. A similar approach is observed in two studies, that based the health states on additional HHFs [34, 39] and a study that based the pathway and difference between strategies on admission rates [33].

3.2.4 Time Horizon and Perspective

The time horizons applied vary greatly across the studies included in this review ranging from 60 days to lifetime. Five of the studies evaluated costs and effects over a lifetime [33, 37, 38, 40, 41] while three studies applied time horizons of <1 year [34, 39, 42]. One study applied a time horizon of 20 years [36]. This is also consistent with the findings of the review by Jafari et al. (2018) in which most studies applied a lifetime horizon and one study used a 20-year time horizon [35]. For the studies applying a time horizon <1 year, two of the studies investigated patients suspected of acute HF in the ED, which could explain the short time horizon [34, 42]. One of the studies applied a healthcare payer perspective and therefore only accounted for costs related to the 6-month follow-up after discharge from the hospital [34]. In fact, the majority of studies applied a healthcare payer perspective when accounting for the costs [33, 34, 36, 37, 40] and only one study applied a societal perspective when accounting for costs [41].

3.2.5 Outcomes

The health outcomes and costs do not vary considerably when comparing which outcomes are included and reported by the different studies. Almost all of the studies included QALY when reporting the base case results [33, 36, 37, 39–41, 43] and the majority of these included QALY as the only health outcome [36–39]. The remaining of these studies included LY as another health outcomes [40, 41]. Two studies did not include QALY as a health outcome, but included outcomes such as hospitalizations, time in hospital per patient, serious adverse events (SAE), and number of echocardiographies [34, 42]. While the majority of studies only reported total costs, two studies reported cost

components such as hospitalization costs, ED costs, diagnostic costs, and drug costs [34, 40].

3.3 Summary

This literature search and review highlights that research on the cost-effectiveness of NT-proBNP is very limited in the T2DM population while different natriuretic peptide strategies are a well-studied area within a broader HF population. Moreover, many studies investigate the cost-effectiveness of natriuretic peptide-guided strategies while the research on screening with NT-proBNP is limited. The studies in this review include either NT-proBNP or BNP while the comparators of the different studies often include diagnosis with clinical assessment and echocardiography. Despite the wide range of models applied, this review shows that the most common model type applied is the Markov model. This is a model type that is also applied in one study investigating screening for HF with NT-proBNP among T2DM patients. The time horizons applied in the different studies range from 60 days to a lifetime, although the majority applied a lifetime horizon. Moreover, the majority of studies applied a healthcare perspective for costs. While there was some variation, QALY was the most common health outcome across all studies. Based on this review it is concluded that natriuretic peptide-guiding strategies in the secondary healthcare sector is a well-studied area of research in Western countries.

In sum, despite well-documented research on the natriuretic peptide-guiding strategies in the secondary healthcare sector, this review shows how there is a lack of research on NT-proBNP screening for HF among T2DM patients in the area of health economic evaluations. To overcome this lack in the current research within health economic evaluations this master's thesis investigates the cost-effectiveness of annual screening with NT-proBNP (cut-off $\geq$400 pg/mL) for HF in a T2DM population in a Danish ambulatory care setting compared to SoC through decision-analytical modeling.

4. Methods

This section will lay out the framework of the decision-analytical model and the methods utilized to undertake this health economic evaluation of annual screening with NT-proBNP (cut-off ≥400 pg/mL) for HF among T2DM patients compared to SoC, consisting of clinical assessment of symptoms and subsequent echocardiography.

4.1 Conceptual Model

This health economic evaluation applies a decision-analytic approach to investigate the cost-effectiveness of annual screening with NT-proBNP measurement of HF among T2DM patients compared to the current diagnostic practice in Danish ambulatory care. A Markov model is developed to simulate the costs and health outcomes in a population of T2DM patients in a Danish ambulatory care setting at risk of developing HF. The study aims to provide a framework that simulates the population of the Thousand&2 cohort. The Thousand&2 Cohort is a Danish cohort established in 2012, in which 1030 T2DM patients were recruited from the ambulatory care centers, SDC, and Center for Diabetes Research (CfD) at Herlev and Gentofte Hospital. Patients in care at SDC and CfD are characterized by inadequately controlled glycaemic levels, co-morbidity, and/or diabetes-related complications. The mean age of patients in the Thousand&2 Cohort is 66,5 years and the age of patients entering the model is therefore assumed to be 66 years [4].

In this analysis, the patients are assumed to attend an annual health check-up at the ambulatory care facility, as guidelines from DCS and the Danish Endocrine Society (DES) recommend assessment of cardiovascular risk factors in T2DM patients at least once a year [19]. The comparator of this analysis is the SoC, the current diagnostic practice, which consists of the assessment of HF symptoms at the annual ambulatory care check-up and subsequent referral for echocardiography in case of present symptoms of HF. The intervention of this analysis is the screening with NT-proBNP cut-off ≥400 pg/mL at the annual ambulatory care check-up and subsequent referral for echocardiography in case of a positive result. In this study, it is hypothesized that the screening with NT-proBNP will increase the number of HF diagnoses among T2DM patients compared to SoC, by screening all patients at annual check-ups in ambulatory care. The primary drivers of the difference between the diagnostic strategies are consequently dependent on the sensitivity and specificity of NT-proBNP ≥400 pg/mL for diagnosing HF in T2DM patients. The sensitivity of NT-proBNP and the probability of developing HF among T2DM patients form the probability of diagnosing HF in T2DM patients in the NT-proBNP strategy. Meanwhile, both the specificity and sensitivity of NT-proBNP are incorporated into the estimation of the resource use related to diagnosing HF in the NT-proBNP strategy.

To estimate the health benefit of the diagnostic strategies, this analysis includes the health outcomes measures quality-adjusted life-year (QALY), life-year (LY), and hospitalization due to HF (HHF). QALY is calculated based on health-state utility values associated with T2DM, HF, and HHF, extracted from literature [44, 45]. By including these health outcomes, the analysis will cover mortality, severity, and overall health burden related to HF and T2DM in a Danish setting. All health outcomes, QALY, LY, and HHF, will be reported, however, only QALY and LY will be included in the ICER calculations. Finally, the model adopts a hospital perspective and applies a mixed costing approach, including both micro-costing and gross-costing [32]. Estimation of resources includes diagnostic tests, treatment for HF, ambulatory care check-ups, and HHF which is considered in the cost estimate, to ensure capturing the full resource consumption related to each of the strategies. The costs are reported in 2024-DKK as diagnostic costs, HHF costs, HF ambulatory care costs, and total costs. To avoid underestimation, costs extracted from the literature have been adjusted for inflation using the consumer price index (adjustments are presented in Appendix C). Both costs and health outcomes are discounted at an annual rate of 3,5% as recommended by the National Institute for Health and Clinical Excellence (NICE) [46]. A WTP threshold of 260.000 DKK/QALY is applied to assess the cost-effectiveness, as recommended by NICE [47].

A Markov model consisting of four health states has been developed in Microsoft® Excel (Version 16.86) to cover the disease progression of HF in T2DM patients in ambulatory care in Denmark. The model framework encompasses the patient's disease progression and each health state is associated with resource consumption and healthcare utilization. All patients in the cohort will enter the model in the health state 'Alive' which includes T2DM patients in ambulatory care at risk of developing HF. Within a cycle of one year, patients can be diagnosed with HF, remain undiagnosed with HF, die, or develop Advanced HF, which requires hospitalization for HF. Patients can transition between the different health states, but can never return to 'Alive' once transitioned to one of the other health states. 'Dead' is an absorbing health state. The model is illustrated in Figure 4.1, and the arrows indicate how patients can transition between health states. The health states and transition probabilities are further described in Sections 4.2.1 and 4.3.1. The complete model is attached as a xlsm-file.

4.2 Model Framework

4.2.1 Health States

As previously mentioned, the Markov model consists of four health states: 'Alive', 'HF', 'Advanced HF', and 'Dead'. The model framework is identical for the NT-proBNP arm and the SoC arm. However, the arms differentiate in diagnostic method which will be outlined in the following. The health state 'Alive' includes T2DM patients in ambulatory care who are not diagnosed with HF. In the SoC

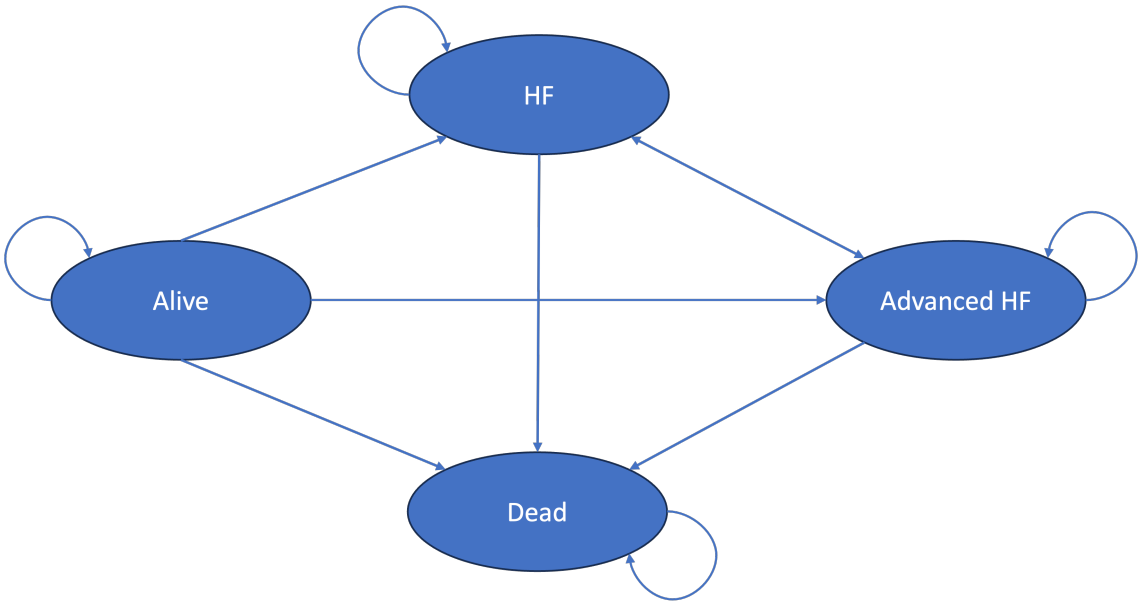

Figure 4.1: *Markov model*

arm of the model, 7,0% of patients develop HF and 9,8% of these patients will develop symptomatic HF and thus be referred for an echocardiography and subsequently be diagnosed with HF. In the NT-proBNP arm all patients in the health state 'Alive' will be screened with NT-proBNP each cycle and the transition probability from 'Alive' to 'HF' in the NT-proBNP arm is dependent on the sensitivity of NT-proBNP at a 400 pg/mL cut-off which is reported to be 81,7% in patients with T2DM [6]. In both arms patients can transition from 'Alive' to 'HF', 'Advanced HF', 'Dead', or stay in 'Alive'. The health state 'HF' includes T2DM patients in ambulatory care who have been diagnosed with HF (including both HFrEF and HFpEF). From 'HF' patients can transition to 'Advanced HF', 'Dead', or stay in 'HF' and these transitions are applicable for both arms in the model. The health state 'Advanced HF' includes T2DM patients hospitalized due to HF. However, it is assumed that patients in 'Advanced HF' will be hospitalized for 10 days during one cycle identical for both arms in the model [48]. From 'Advanced HF' patients can transition to 'Dead', 'HF', or they can be rehospitalized due to HF and hereby remain in 'Advanced HF'.

4.3 Model Input

The estimated transition probabilities applied in the model are based on results from various studies investigating different outcomes related to T2DM and HF and the diagnostic accuracy of NT-proBNP for HF among patients with T2DM [6, 41, 49–53]. Furthermore, a background mortality for the general population is applied to ensure that age-related mortality is reflected in the model. This background mortality is based on the 2020-2022 life expectancy reported by the UK National Office for National Statistics [54]. The costs are estimated based on studies, and diagnosis-related group (DRG) tariffs [3, 48, 55]. Utility inputs are based on studies reporting health state utility values for

T2DM, HF, and hospitalization due to HF [44, 45]. All model inputs are presented in table 4.1. Calculations of transition probabilities, costs, and health state utility values (HSUV) are presented in Appendix A, B, and C, respectively.

4.3.1 Transition Probabilities

4.3.1.1 From 'Alive'

In the SoC arm the transition probability from 'Alive' to 'HF' is based on the incidence rate HF among patients with T2DM (7,0%) [56] and the annual probability of developing symptoms of HF when untreated for HF (9,8%) [41]. Thus, the transition probability from 'Alive' to 'HF' in the SoC arm is 0,7%. In the NT-proBNP arm the probability of transitioning from 'Alive' to 'HF' is based on the probability of developing HF when diagnosed with T2DM (7,0%) [56] and the sensitivity of NT-proBNP with a cut-off value of $\geq$400 pg/mL (81,7%) [6]. The remaining 18,3% (the false negatives) will remain in the health state 'Alive'. Based on these parameters, the transition probability from 'Alive' to 'HF' applied in the NT-proBNP arm is 5,7%. The transition probability from 'Alive' to 'Advanced HF' is based on the study by Cavender et al. (2015), which found a 4-year rate of hospitalization due to HF among T2DM patients [50]. Conversed to 1-year probability the transition probability applied in this model is 2,4%. The probability of transitioning from 'Alive' to 'Dead' is based on the study by Barkoudah et al. (2012), which found a 1-year probability of death from any cause of 1,83% among T2DM patients treated with SoC rather than sodium-glucose co-transporter 2 inhibitor (SGLT2i) [51]. The probabilities of transitioning from 'Alive' to 'Advanced HF' and 'Dead' are identical between the strategies. However, asymptomatic T2DM patients with HF in the SoC arm and false negatives in the NT-proBNP arm are assumed to have probabilities of transitioning from 'Alive' to 'Advanced HF' and 'Dead' of 2,4% and 1,83%. These are the same probabilities applied for T2DM patients in the health state 'HF' although the asymptomatic and false negative patients have not received treatment for HF, although a difference between the treated and untreated patients with HF would be expected. The probability of staying in 'Alive' is the residual equalling 95% and 90% for SoC and NT-proBNP, respectively. All of the abovementioned transition parameters and probabilities are listed in table 4.1. Calculations are presented in Appendix A.

4.3.1.2 From 'HF'

In both arms of the model patients can transition from 'HF' to either 'Advanced HF', 'Dead', or stay in 'HF'. In both the NT-proBNP and the SoC arms the probability of transitioning from 'HF' to 'Advanced HF' is based on the study by Cavender et al. (2015), which found that at 4-year follow-up hospitalization due to HF was associated with a history of HF and T2DM at baseline with an adjusted odds ratio (OR) of 4,72 corresponding to a 1-year probability of 35,5% [50]. The probability of transitioning from 'HF' to 'Dead' is based on a study by Johansson et al. (2014) which found a 5-year

Table 4.1: *Model input*

Transition probabilities		
	Probability	**Source**
SoC-specific transition probabilities		
From 'Alive' to 'Alive'	0,950	Residual
From 'Alive' to 'HF'	0,007	[41, 56]
NT-proBNP-specific transition probabilites		
From 'Alive' to 'Alive'	0,900	Residual
From 'Alive' to 'HF'	0,057	[6, 56]
General transition probabilites		
From 'Alive' to 'Dead'	0,018	[51]
From 'Alive' to 'Advanced HF'	0,024	[50]
From 'HF' to 'HF'	0,483	Residual
From 'HF' to 'Advanced HF'	0,353	[50]
From 'HF' to 'Dead'	0,163	[52]
From 'Advanced HF' to 'Advanced HF'	0,250	[53]
From 'Advanced HF' to 'HF'	0,400	Residual
From 'Advanced HF' to 'Dead'	0,350	[53]
Costs		
	Cost (DKK)	**Source**
Health state costs (annual)		
Alive	23.777	[3]
HF	82.548	[3]
Advanced HF	149.916	[3, 48]
Diagnostic costs		
Echocardiography	2.026	[55]
NT-proBNP	264	[57]
Treatment costs (annual)		
SoC	5.259	[3]
Utility		
	Utility	**Source**
Health state utilities		
Alive	0,752	[44]
HF	0,591	[44]
Advanced HF	0,587	[44, 45]
Annual utility decrement		
Annual utility decrement T2DM + HF	-0,046	[58]
Annual utility decrement T2DM	-0,011	[58]
Other input		
	Input	**Source**
Mean age for entering the model	66	[4]
Sensitivity and specificity		
NT-proBNP $\geq$400 pg/mL sensitivity	81,70%	[6]
NT-proBNP $\geq$400 pg/mL specificity	80,30%	[6]
Probability of developing HF with T2DM	7,00%	[56]
Probability of developing symptoms of HF	9,80%	
Annual discount rate	3,50%	[46]

mortality rate of 58% among patients with T2DM and HF aged 66-80 years [52]. This corresponds to a 1-year probability of 15,9%. The probability of staying in 'HF' is the residual equalling 48,3%. All of the above-mentioned transition probabilities are listed in table 4.1. Calculations are presented in Appendix A.

4.3.1.3 From 'Advanced HF'

The probabilities of transitioning from 'Advanced HF' to 'Advanced HF' and 'Dead' are based on a study by Freedman et al. (2022) [53]. The study reported that 25% of patients hospitalized due to HF were re-hospitalized within 1 year after discharge and 35% died from any cause within 1 year [53]. Hereby, the probability of staying in 'Advanced HF' is 25%, and the probability of transitioning to 'Dead' is 35%, while the probability of transitioning back to 'HF' is the residual equalling 40%. Calculations are presented in Appendix A.

4.3.2 Costs

4.3.2.1 Health State Costs

The health state costs are derived from the study by Sortsø et al. (2016), investigating the societal costs of DM in Denmark, and the study by Bundgaard et al. (2019), investigating the economic burden of HF in Denmark [3, 48]. Sortsø et al. (2016) applied a societal cost perspective, including both direct and indirect costs, and evaluated different cost components on an individual level [3]. In this current study, the reported secondary healthcare costs are applied in the model. The secondary care costs component reported by Sortsø et al. (2016) includes secondary healthcare services, including ambulatory care and emergency room visits, and is calculated based on 2012 DRG tariffs [3]. Sortsø et al. (2016) found that the total cost per person-year for DM patients without complications associated with secondary care was 23.777 DKK. Sortsø et al. (2016) also found that the total cost per person-year for DM patients with major complications (including HF) associated with secondary care was 82.548 DKK [3]. In this current study, the cost for DM patients with major complications is assumed to be equivalent to T2DM patients with HF and therefore applied to the health state 'HF'. The costs associated with no complications are applied to the health state 'Alive'. The study by Bundgaard et al. (2016) found that the average annual direct cost related to inpatient admissions among patients with HF amounted to 67.368 DKK, with a length of hospital stay ranging between 4 and 20 days. This includes both direct and indirect costs [48]. The cost of 'Advanced HF' is based on the cost associated with hospitalization due to HF from Bundgaard et al. (2016) and the total cost per person-year for DM patients with major complications from Sortsø et al. (2016) [3, 48]. Pharmaceutical treatment for HF is dependent on the LVEF and thus the type of HF; HFpEF or HFrEF. Treatment includes SGLT2-i, or glucagon-like peptide 1 (GLP-1), angiotensin-converting-enzyme (ACE) inhibitors, and beta-blockers among others [11, 19]. In the current analysis, the cost associated with pharmaceutical treatment of

HF is defined as treatment costs. The treatment costs are extracted from the study by Sortsø et al. (2016) which reports pharmaceutical costs per person-year of 623€ and 1.218€ for patients with no and major complications, respectively [3]. Due to the large variation in types and dosage of pharmaceutical treatments the treatment costs in the current analysis are assumed to be equivalent to the costs only related to major complications and are thus calculated by $1.218 - 623 = 595$€ (2016 value). All costs are converted from € to DKK and adjusted for inflation using the consumer price index (CPI), for calculations see Appendix C, and the costs applied in the base case analysis are presented in Table 4.1.

4.3.2.2 Diagnostic Costs

The cost related to the diagnostic tools NT-proBNP and echocardiography are applied differently between the arms in the model. The cost of one echocardiography is estimated to be 2.026 DKK, based on the 2024 DRG tariff 05PR04 [55]. In the SoC arm, this cost is applied in each cycle for patients in the 'Alive' health state who develop HF and symptoms of HF. In the NT-proBNP arm, the echocardiography cost is applied for patients receiving a positive NT-proBNP result ($\geq$400 pg/mL). This includes both true and false positives. The cost of an NT-proBNP test is estimated to be 264 DKK based on tariffs from the Clinical Biochemical Department at Bispebjerg Hospital from 2024 [57]. The NT-proBNP cost is applied only in the NT-proBNP arm and for all patients in the 'Alive' health state each cycle.

4.3.3 Utility

The current analysis uses health-related quality of life (HRQoL)-measures to calculate HSUV when the population has comorbidities. HRQoL data is extracted from Hvidberg et al. (2023), which utilized the EQ-5D-3L instrument to assess HRQoL among a Danish population, to define chronic conditions based on ICD-10 codes. The EQ-5D-3L describes 5 different health dimensions at 3 different levels and by applying national preference-based utility weights the EQ-5D can be combined into a single utility score. The utility scores reported in the study have an upper limit of 1, representing perfect health, while negative values represent health states considered worse than death, and 0 represents death. The extracted HSUV for the health state 'Alive' is at 0,752, while the health state 'HF' is at 0,678 [44]. To calculate the HSUV with comorbidities, this analysis uses the multiplicative method presented by Ara et al. (2017) [59]. The needed values to utilize the multiplicative way is a population with no history of T2DM, no history of HF, and no history of either condition. The extracted value for the population with no history of either T2DM or HF is assumed to be 0,974 since the population has no health-related problems (SF-12). Patients with no history of T2DM and HF are considered to have an HSUV equal to those who have no chronic conditions since both disease areas are considered chronic conditions [44]. Utilizing the multiplicative method to derive HSUV for

comorbidities, the estimated HSUV for the health state HF is calculated to be 0,591 (Appendix B).

To calculate the HSUV for the 'Advanced HF' health state, this analysis uses utility values reported by Gu et al.(2020) [45]. The study investigates the HRQoL for T2DM patients when being hospitalized due to complications and the study reports a mean HSUV for HHF for T2DM patients at 0,47 and a mean HSUV for T2DM with HF at 0,591 [45]. When considering a hospitalization duration of 10 days, and a cycle length of 1 year, the adjusted HSUV for 'Advanced HF' is calculated to be 0,5873 [45]. To account for the time-dependent disutility related to the duration of T2DM and HF, utility decrements from a study by Keng et al. (2002) are applied [58]. The study examines utility decrements in a diabetic population and estimates an annual utility decrement of -0,0046 for T2DM and -0,011 for HF when considering a diabetes duration of 10 to 15 years. [58]. Calculations are presented in Appendix B.

4.4 Sensitivity Analysis

A one-way DSA is conducted to explore the uncertainties of the parameters and their impact on the ICER. The parameters of interest include an upper and lower bound, which is defined as a confidence interval (CI), only if available. For the parameters that are not provided with CI by the literature, the upper and lower bounds parameter value was adjusted by $\pm$25% for both ends. The cost for the health states 'Alive', 'HF', and 'Advanced HF', and the cost treatment for HF, echocardiography, and NT-proBNP are adjusted with a 25% at upper and lower bounds. The upper and lower bound for the probability of developing HF and NT-proBNP specificity and sensitivity at a cut-off of $\geq$400 pg/mL is based on their respective 95% CIs [6, 56]. The probability for developing symptoms of HF was applied with a 25% at the upper and lower bound. The upper and lower bounds of the parameters are presented in Table 4.3.

To further investigate the parameter uncertainty as well as the decision uncertainty a PSA is conducted. The standard errors (SE) of the parameters are defined as either $\pm$25% or the 95% CIs which are also applied in the one-way DSA. All probabilities, sensitivity, specificity, and utility values are assumed to be beta-distributed, while disutility values for T2DM and HF are assumed to be Log-normal distributed. All costs are assumed to be gamma-distributed. The PSA will produce 10.000 iterations which will be presented in an ICE scatterplot. The probability of cost-effectiveness depending on the cost-effectiveness threshold will be illustrated in a CEAC.

To investigate the uncertainties related to specific parameters three different scenario analyses are conducted. The first scenario analysis investigates the impact on the ICER when changing the cut-off of NT-proBNP and hereby the sensitivity and specificity of the test. In scenario 1 the NT-proBNP cut-off is changed to $\geq$125 pg/mL with a sensitivity of 94,6% and a specificity of 50% [6]. In scenario

2 the NT-proBNP cut-ff is changed to >2000 pg/mL with a sensitivity of 38,9% and a specificity of 96,1% [6]. The second scenario analysis investigates the impact of the mean age for patients entering the model. This analysis includes three scenarios with mean ages of 60, 70, and 80 years. The study by Johansson et al. (2014) showed a 5-year mortality rate among T2DM patients with HF of 59 in the age group ≥65 years. In the age groups 66-80 years and >80 years the 5-year mortality rates are 58 and 84, respectively [52]. These mortality rates were applied for the mean ages of entering the model of 60, 70, and 80 years. The 1-year mortality rate and probability of transitioning from 'HF' to 'Dead' applied for age 60 is thus 0,163. For age 70 this rate is assumed to be 0,159 and 0,307 for age 80 years [52]. In this scenario analysis, the baseline mortality of death is also age-dependent and will increase with age [54]. The last scenario analysis is a two-way sensitivity analysis, including NT-proBNP cut-offs of ≥125 pg/mL, ≥400 pg/mL, and >2000 pg/mL and mean ages for entering the model of 60, 66, 70, and 80 years producing 12 different ICERs in total. Table 4.2 provides an overview of the different scenario analyses, including the parameters investigated and values applied.

Table 4.2: *Scenario analyses overview*

	Parameter	Values applied		Source
		Sensitivity	**Specificity**	
Scenario 1	NT-proBNP ≥125 pg/mL	94,60%	50,00%	[6]
Scenario 2	NT-proBNP 2000 pg/mL	38,90%	96,10%	[6]
		TP from 'HF' to 'Dead'		
Scenario 3	Mean age of 60 years	0,163		[52]
Scenario 4	Mean age of 70 years	0,159		[52]
Scenario 5	Mean age of 80 years	0,307		[52]
Two-way sensitivity analysis	NT-proBNP cut-off values: ≥125 pg/mL, ≥400 pg/mL, and >2000 pg/mL **and** Mean ages of: 60 years, 66 years, 70 years, and 80 years	Sensitivity and specificity specific for NT-proBNP cut-off value **and** TP from 'HF' to 'Dead' specific for mean ages (see above and Table 4.1)		[6, 52]

Table 4.3: *Parameter values and distributions for sensitivity analyses*

Parameter	Mean	SE/95%CI	Distribution	Alpha	Beta	Source
TP from 'Alive' to 'Advanced HF'	0,024	0,006	Beta	15,59	623,77	[50]
TP from 'Alive' to 'Dead'	0,018	0,005	Beta	15,69	841,63	[51]
TP from 'HF' to 'Advanced HF'	0,353	0,088	Beta	9,99	18,28	[50]
TP from 'HF' to 'Dead'	0,159	0,040	Beta	13,29	70,16	[52]
TP from 'Advanced HF' to 'Advanced HF'	0,250	0,063	Beta	11,75	35,25	[53]
TP from 'Advanced HF' to 'Dead'	0,350	0,088	Beta	10,05	18,66	[53]
Probability of developing HF	0,070	0,04-0,11	Beta	14,22	188,93	[56]
Probability of developing symptoms	0,098	0,025	Beta	14,33	131,93	[41]
NT-proBNP cut-off $\geq$400 pg/mL sensitivity	0,817	0,81-0,823	Beta	208.556,21	46.714,55	[6]
NT-proBNP cut-off $\geq$400 pg/mL specificity	0,803	0,8-0,805	Beta	78.077,33	19.154,71	[6]
Health state utility 'Alive'	0,752	0,188	Beta	3,22	1,06	[44]
Health state utility 'HF'	0,591	0,148	Beta	5,96	4,13	[44]
Health state utility 'Advanced HF'	0,587	0,147	Beta	6,02	4,23	[44, 45]
Annual utility decrement for T2DM and HF	0,046	0,012	Log-normal	N/A	N/A	[58]
Annual utility decrement for T2DM	0,011	0,003	Log-normal	N/A	N/A	[58]
Health state cost 'Alive'	23.777	5.944	Gamma	16	1.486	[3]
Health state cost 'HF'	82.548	20.637	Gamma	16	5.159	[3]
Health state cost 'Advanced HF'	149.916	37.479	Gamma	16	9.370	[3, 48]
NT-proBNP test cost	264	66	Gamma	16	17	[57]
Echocardiography cost	2.026	507	Gamma	16	127	[55]
Treatment for HF cost	5.259	1.315	Gamma	16	329	[3]

5. Results

In the following section I will present the results of the cost-effectiveness analysis, including the base case analysis and the various sensitivity analyses.

5.1 Base Case Cost-effectiveness Analysis

The base case discounted model results per patient are presented in Table 5.1. The NT-proBNP strategy results in an average total cost per patient of 121.665 DKK. The majority of costs are comprised of HF ambulatory care costs, which amount to 43.534 DKK. Meanwhile, diagnostic costs comprise only 1.998 DKK of the total costs and costs related to HHF amount to 12.893 DKK. The SoC strategy results in an average total cost per patient of 124.720 DKK and the costs related to HF ambulatory care amount to 41.994 DKK. Meanwhile, costs related to diagnostics and HHF amount to 506 DKK and 18.815 DKK, respectively. When comparing the costs of the NT-proBNP strategy to the SoC strategy, the average incremental HF ambulatory care cost per patient is 1.540 DKK. The average incremental diagnostic cost per patient is 1.492 DKK, while the average incremental HHF cost per patient is -5.922 DKK. Consequently, there are additional diagnostic and HF ambulatory care costs when applying the NT-proBNP strategy compared to the SoC strategy. However, the NT-proBNP strategy is associated with fewer costs related to HHF. The average incremental total cost per patient subsequently amounts to -3.055 DKK and the NT-proBNP strategy is overall cost-saving compared to the SoC strategy.

Table 5.1: *Base case model results per patient*

	NT-proBNP	**SoC**	**Incremental**
Costs (DKK)			
Diagnostic costs	1.998	506	1.492
HHF costs	12.893	18.815	-5.922
HF ambulatory costs	43.534	41.994	1.540
Total costs	**121.665**	**124.720**	**-3.055**
Health outcomes			
LYs	3,17	3,04	0,12
HHFs	0,19	0,32	-0,13
QALYs	**2,4042**	**2,3068**	**0,0974**

The average health outcomes per patient are also presented in Table 5.1. The NT-proBNP strategy results in 0,19 HHF, 3,17 LYs, and 2,4042 QALY per patient. The SoC strategy results in 0,32 HHF, 3,04 LY, and 2,3068 QALY. This produces average incremental per-patient health outcomes of -0,13 HHF, 0,12 LY, and 0,0974 QALY. The NT-proBNP strategy is therefore associated with additional QALY and LYs when compared to the SoC strategy. Moreover, the NT-proBNP is also associated with fewer HHFs compared to SoC. Overall, the base case model results indicate that screening with NT-proBNP at a cut-off at ≥400 pg/mL compared to SoC results in fewer total costs and HHFs and additional diagnostic costs, while increasing LYs and QALYs.

The ICERs are presented in Table 5.2, which show that when comparing NT-proBNP ≥400 pg/mL screening to the SoC strategy 24.894 DKK is saved per LY gained. Moreover, a total cost of 26.293 DKK is saved per QALY gained. When applying a cost-effectiveness threshold of 260.000 DKK/QALY the screening with NT-proBNP ≥400 pg/mL in this population and setting is cost-effective compared to the SoC strategy.

Table 5.2: *Base case cost-effectiveness results*

ICERs		
Total cost per LY	-24.894	DKK/QALY
Total cost per QALY	-31.359	DKK/QALY

The incremental cost-effectiveness plane illustrates that the ICER is placed in the southeast quadrant, below the cost-effectiveness threshold, showing that the screening with NT-proBNP ≥400 pg/mL compared to SoC is both cost-saving and increases health benefit and therefor NT-proBNP ≥400 pg/mL is dominant compared to SoC (Figure 5.1).

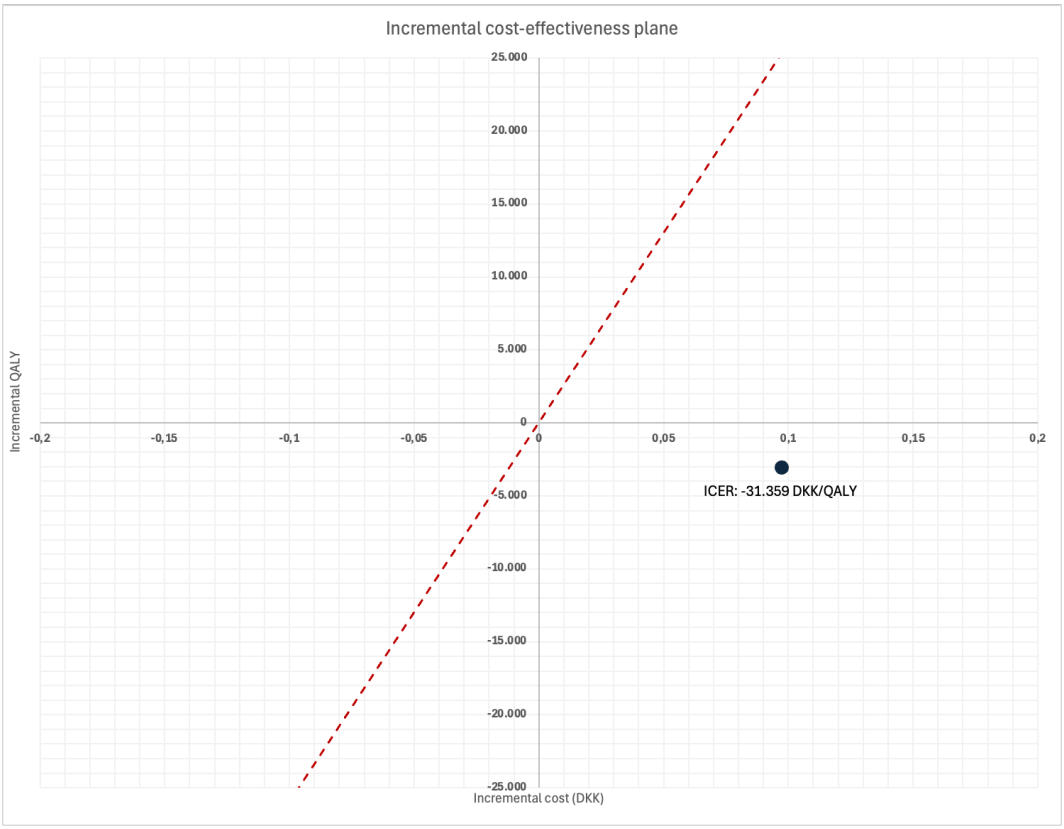

Figure 5.1: *Base case incremental cost-effectiveness plane*

5.2 Sensitivity Analyses

5.2.1 One-way Deterministic Sensitivity Analysis

A one-way DSA was conducted and visualized as a tornado plot, with sought-out parameters of interest. Figure 5.2, shows the results of the one-way DSA for the NT-proBNP ≥400 pg/mL strategy compared to the SoC strategy and incorporates parameters with their respective lower and upper bounds. The one-way DSA considers the discounted base case results of the ICER at -31.359 DKK/QALY. The results of the one-way DSA show that the model is most sensitive to the uncertainty related to the health state cost of 'Advanced HF', with an ICER ranging from -81.461 DKK/QALY to 18.743 DKK/QALY. Costs related to 'HF' and the transition probability from 'Advanced HF' to 'Dead' also have a relatively high impact on the ICER, while the sensitivity of NT-proBNP ≥400 pg/mL, probability of developing HF, and the annual utility decrements have the least impact on the ICER. While the impact of the parameters differentiates very much, the ICERs remain below the threshold of 260.000 DKK/QALY and therefore remain cost-effective. The four parameters with the least impact on the ICER have been excluded from the tornado plot illustrated in figure 5.2. A tornado plot including all parameters is presented in Appendix D.

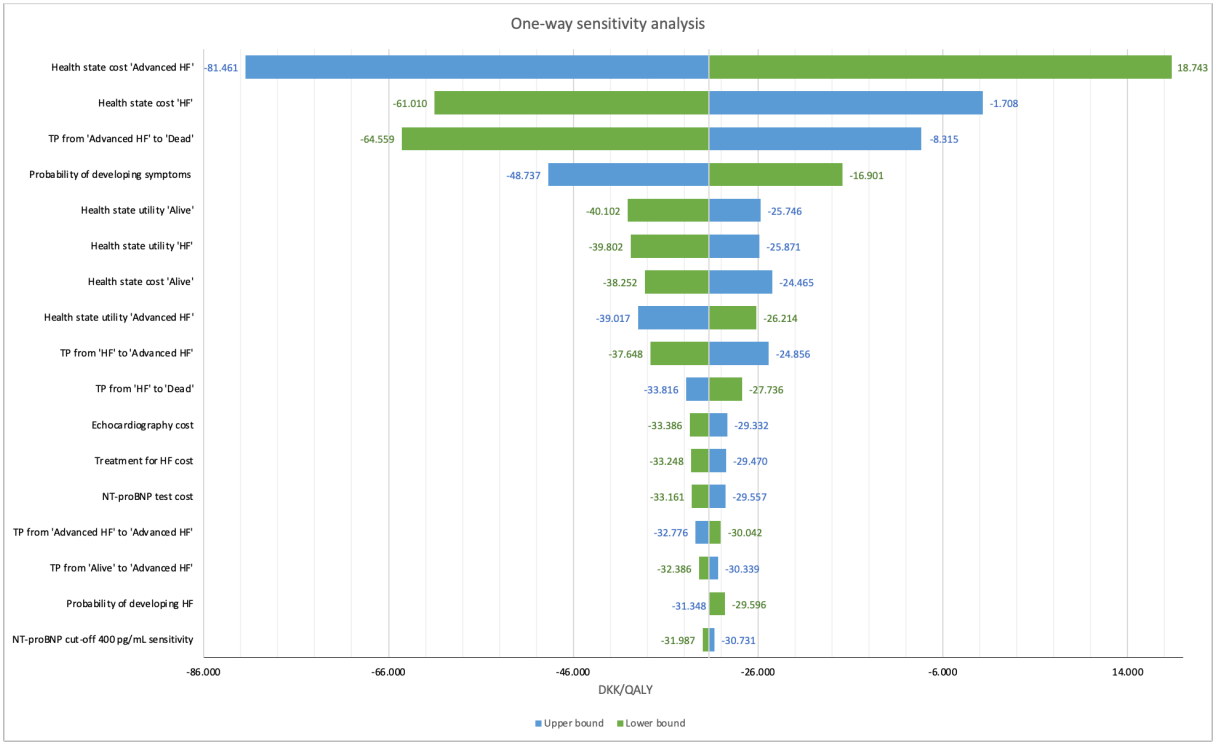

Figure 5.2: *Tornado plot depicting the one-way sensitivity analysis*

5.2.2 Probabilistic Sensitivity Analysis

The PSA produced 10.000 iterations investigating the impact of all parameter uncertainties simultaneously. The average costs and QALYs of these iterations are presented for each arm and as incremental values in Table 5.3. The average incremental total costs and QALYs are -3.024 and 0,0969, respectively. This produces an average ICER of -31.208 DKK/QALY. Moreover, the PSA shows that when applying a cost-effectiveness threshold of 260.000 DKK/QALY there is a 95,55% probability of NT-proBNP being cost-effective compared to SoC.

Table 5.3: *PSA results*

	NT-proBNP	**SoC**	**Incremental**
Total cost per patient	121.710	124.734	-3.024
QALY gain per patient	2,4099	2,3127	0,0969
ICER			-31.208
Probability that NT-proBNP is cost-effective at 260.000DKK per QALY			95,55%

The incremental cost-effectiveness scatterplot (Figure 5.3) illustrates the 10.000 iterations (blue) produced by the PSA compared to the base-case ICER (orange). The majority of iterations are placed below the cost-effectiveness threshold of 260.000 DKK/QALY. Moreover, a substantial proportion of the cost-effective iterations are placed in the southeast quadrant in which NT-proBNP is dominant compared to SoC as NT-proBNP $\geq$400 pg/mL is both cost-saving and increases health benefits.
The CEAC (Figure 5.4) illustrates the probability of the NT-proBNP $\geq$400 pg/mL strategy being cost-effective compared to the SoC strategy at different cost-effectiveness thresholds ranging from 0 DKK/QALY to 500.000 DKK/QALY. The NT-proBNP and SoC curves cross at a threshold of approximately 50.000 DKK/QALY, at which threshold the NT-proBNP and SoC strategies have equal probability of being cost-effective. At a cost-effectiveness threshold of 260.000 DKK/QALY the NT-proBNP $\geq$400 pg/mL strategy has a 95,55% probability of being cost-effective while the SoC strategy has a 4,45% probability of being cost-effective. The CEAC illustrates that when increasing the cost-effectiveness threshold the probability of NT-proBNP $\geq$400 pg/mL being cost-effective increases.

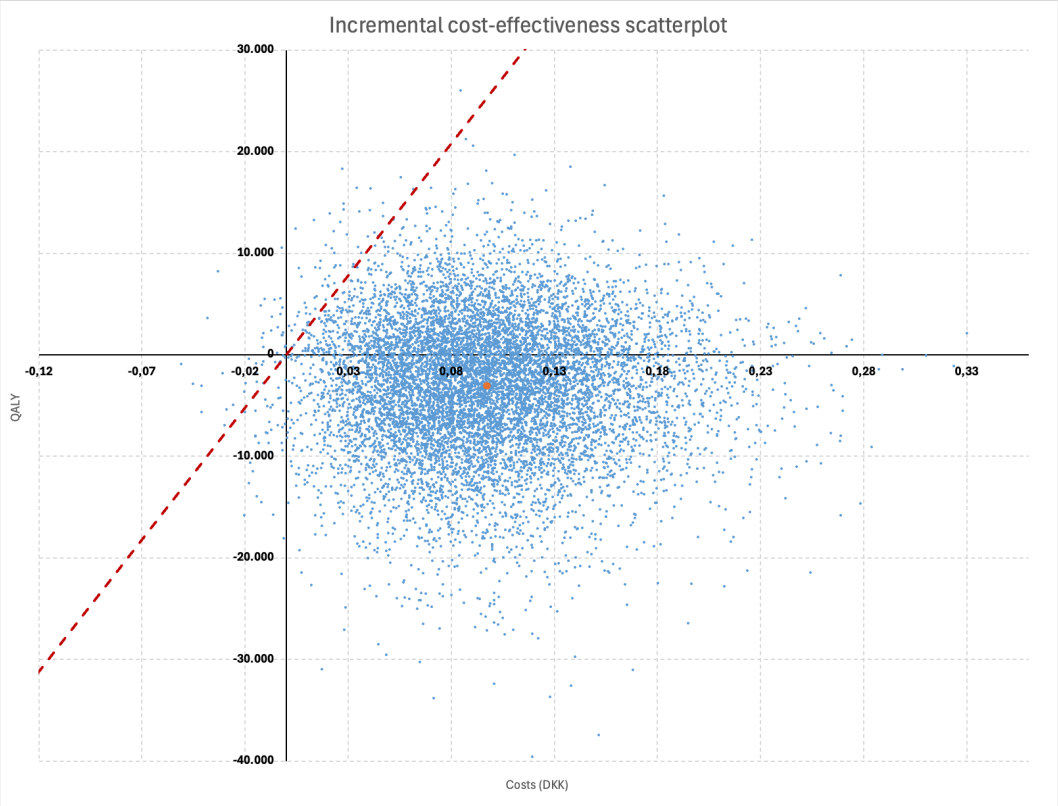

Figure 5.3: *PSA incremental cost-effectiveness scatterplot*

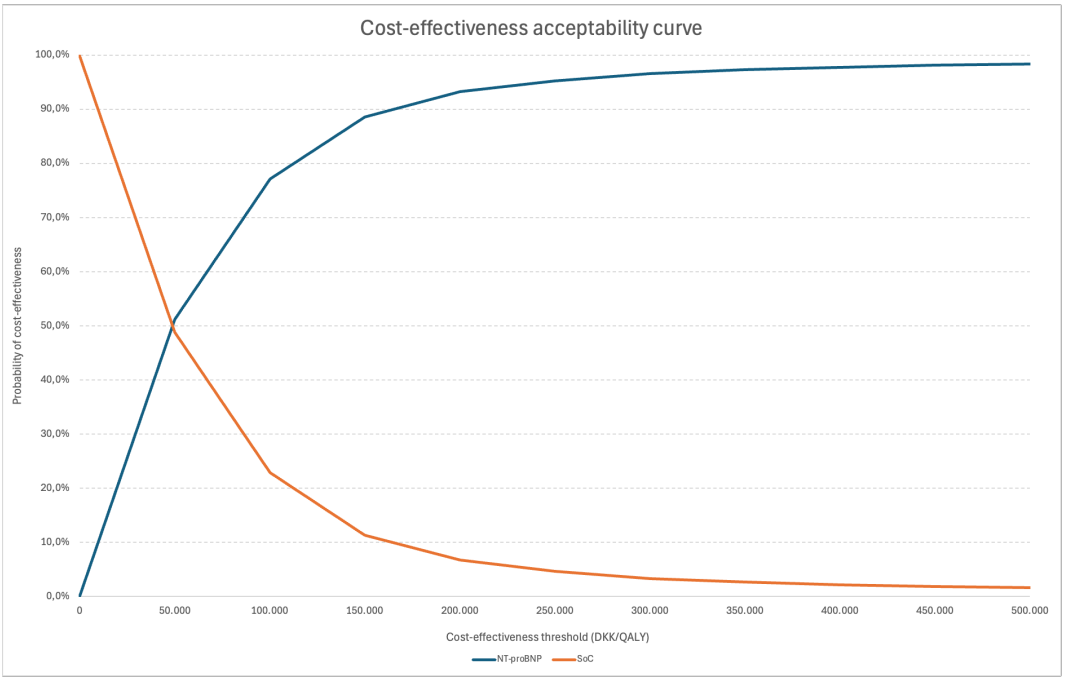

Figure 5.4: *Cost-effectiveness acceptability curve*

5.2.3 Scenario Analyses

Two different scenario analyses and a two-way sensitivity analysis were performed to investigate the impact of NT-proBNP cut-off and mean age on the model results.

5.2.3.1 NT-proBNP Cut-off Scenario Analysis

The scenario analysis investigating the impact of NT-proBNP cut-off on the model results, was performed by applying a cut-off of ≥125 pg/mL in Scenario 1 and a cut-off of >2000 pg/mL in Scenario 2. In Scenario 1 with an NT-proBNP cut-off ≥125 pg/mL, the NT-proBNP strategy is more costly compared to the SoC strategy with an incremental total cost of 801 DKK but more effective compared to SoC in terms of HHFs averted, LYs gained, and QALYs gained. With an ICER of 8.212 DKK/QALY, NT-proBNP ≥125 pg/mL is cost-effective when applying a cost-effectiveness threshold of 260.000 DKK/QALY compared to the SoC strategy. In Scenario 2 with an NT-proBNP cut-off of >2000 pg/mL the incremental total cost is -11.938 DKK indicating that the NT-proBNP >2000 pg/mL strategy is more cost-saving compared to the SoC strategy. When comparing the incremental cost components, the HHF costs saved are similar between Scenario 1 and 2. Meanwhile, the difference in additional HF ambulatory care costs is more noticeable at 4.578 DKK for Scenario 1 and -8.867 DKK for Scenario 2. When looking at the health outcomes, the NT-proBNP >2000 pg/mL strategy is also more effective across the majority of health outcomes with more HHFs averted, more LYs gained, and more QALYs gained. The ICER of -123.832 DKK/QALY shows that the cost per QALY is lower for the NT-proBNP >2000 pg/mL strategy compared to the SoC strategy. The results of the NT-proBNP cut-off scenario analysis are presented in Table 5.4.

The ICERs (total cost/QALY) of the NT-proBNP cut-off scenario analysis are presented alongside the base-case ICER in Figure 5.5. The base case ICER of -26.293 DKK/QALY and the Scenario 2 (NT-proBNP >2000 pg/mL) ICER of -123.832 DKK/QALY are placed in the southeast quadrant, making NT-proBNP at both cut-off values dominant compared to SoC. Meanwhile, Scenario 1 (NT-proBNP ≥125 pg/mL) ICER is placed in the northeast quadrant illustrating that NT-proBNP ≥125 pg/mL is both more costly and more effective compared to SoC. While the NT-proBNP cut-off of ≥125 pg/mL is less cost-effective than NT-proBNP cut-offs of ≥400 pg/mL and >2000 pg/mL, it is still below the cost-effectiveness threshold of 260.000 DKK/QALY. Moreover, the cost-effectiveness plane shows that the three NT-proBNP cut-off strategies vary primarily in incremental cost and less so in incremental QALYs.

Table 5.4: *Scenario analysis (NT-proBNP cut-off ≥125 pg/mL and >2000 pg/mL)*

Scenario 1: NT-proBNP cut-off ≥125 pg/mL			
	NT-proBNP	**SoC**	**Incremental**
Costs (DKK)			
Diagnostic costs	3.523	506	3.018
HHF costs	12.923	18.815	-5.892
HF ambulatory costs	46.571	41.994	4.578
Total costs	125.521	124.720	801
Health outcomes			
LYs	3,17	3,04	0,13
HHFs	0,19	0,32	-0,13
QALYs	2,4044	2,3068	0,0976
ICERs			
Total cost per LY		6.344	DKK/LY
Total cost per QALY		8.212	DKK/QALY

Scenario 2: NT-proBNP cut-off >2000 pg/mL			
	NT-proBNP	**SoC**	**Incremental**
Costs (DKK)			
Diagnostic costs	1.086	506	580
HHF costs	12.809	18.815	-6.006
HF ambulatory costs	33.127	41.994	-8.867
Total costs	112.781	124.720	-11.938
Health outcomes			
LYs	3,15	3,04	0,11
HHFs	0,19	0,32	-0,13
QALYs	2,4032	2,3068	0,0964
ICERs			
Total cost per LY		-108.478	DKK/LY
Total cost per QALY		-123.832	DKK/QALY

5.2.3.2 Mean Age Scenario Analysis

To investigate the impact of age on the cost-effectiveness of the NT-proBNP strategy with a cut-off of ≥400 pg/mL compared to the SoC strategy, a scenario analysis was conducted applying three different mean ages of entering the model. In scenario 3 the mean age for entering the model is 60 years, which results in an incremental total cost of -3.443 DKK when comparing the NT-proBNP ≥400 pg/mL strategy and the SoC strategy. When looking at each of the cost components, the incremental HHF cost is -6.878 DKK while the incremental HF ambulatory care costs amount to 1.821 DKK, meaning that the NT-proBNP strategy is cost-saving overall even though the costs related to HF ambulatory care are increased. In health outcomes, the incremental values are -0,15 HHFs, 0,15 LYs, HF, and 0,1182 QALYs. This produces an ICER (total cost/QALY) for Scenario 3 of -29.132

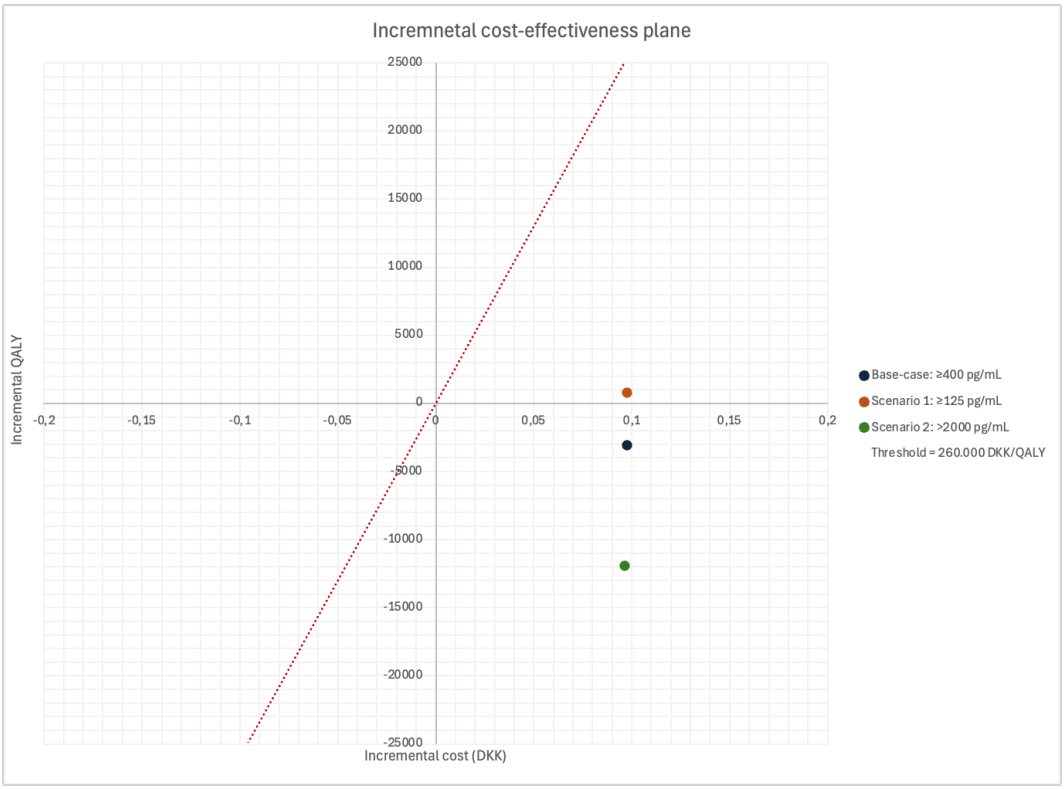

Figure 5.5: *Scenario analysis cost-effectiveness plane (NT-proBNP cut-off)*

DKK/QALY. In Scenario 4 the mean age for entering the model is 70 years, which results in an incremental total cost of -2.800 DKK, -0,11 HHFs, 0,10 LYs, and 0,0789 QALYs. The ICER amounts to -35.081 DKK/QALY. Scenario 5 applied a mean age of 80 years. In this scenario, the incremental costs and health outcomes are a total cost of -2.520 DKK, -0,14 HHFs, 0,06 LYs, and 0,0446 QALYs resulting in an ICER of -56.457 DKK/QALY. When looking at the incremental HF ambulatory costs, Scenario 5 is different from the previous scenarios in this analysis as the NT-proBNP strategy results in fewer cases of HF diagnosed and thus fewer patients in the 'HF' health state. The costs, health outcomes, incremental values, and ICERs in Scenarios 3-5 are presented in Table 5.5.

The ICERs (DKK/QALY) of the scenario analysis investigating the mean age of the population is presented in Figure 5.6. The ICE plane shows that ICERs for Scenarios 4 and 5 are placed in the southeast quadrant and hereby dominant because the NT-proBNP strategy is a cheaper and more effective alternative to the SoC strategy at mean ages of 70 and 80 years. The ICER of Scenario 3 is placed in the northeast quadrant as the NT-proBNP strategy at this mean age is more costly, but also more effective than the SoC strategy. However, when applying a cost-effectiveness threshold of 260.000 DKK/QALY all three scenarios are cost-effective. When comparing the ICERs presented in the ICE plane, Scenario 3 is the most costly but also produces more health gain. This is compared to Scenario 5 which is the least costly, but the least effective. However, the ICER of Scenario 5 indicates

that this mean age is the most cost-effective compared to 3 and 4, as this has the lowest ICER and consequently produces more value for money.

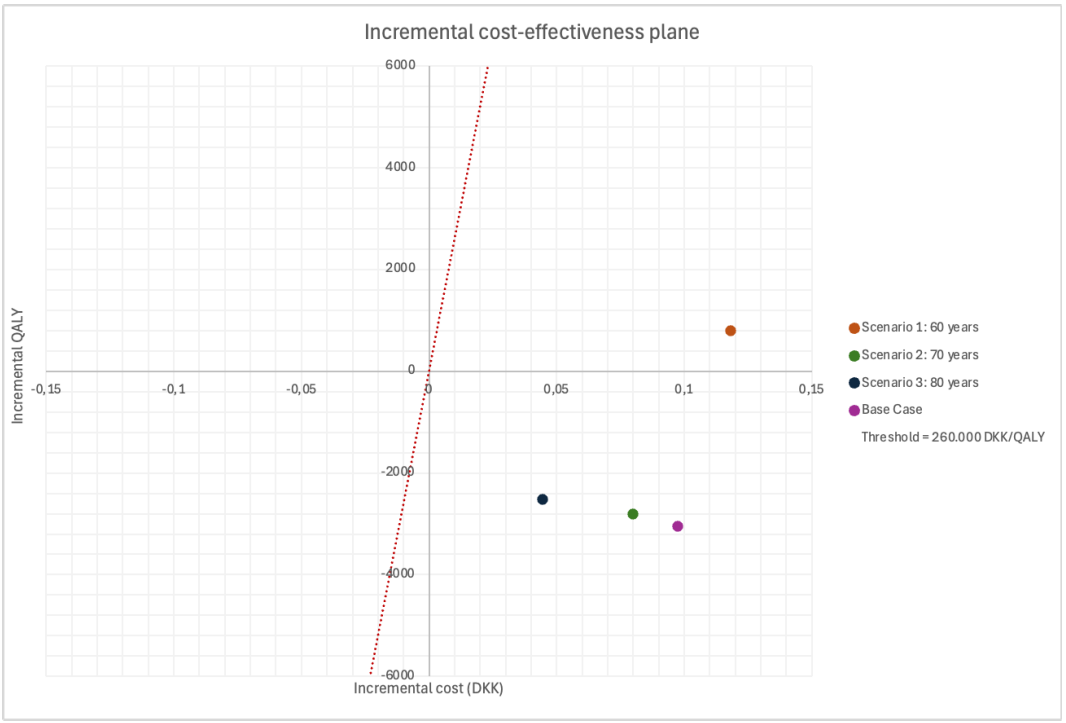

Figure 5.6: *Scenario analysis incremental cost-effectiveness plane (Mean age)*

Table 5.5: *Scenario analysis (Mean age of 60, 70, and 80 years)*

Scenario 3: Mean age 60 years			
	NT-proBNP	**SoC**	**Incremental**
Costs (DKK)			
Diagnostic costs	2.325	587	1.738
HHF costs	15.431	22.309	-6.878
HF ambulatory costs	51.926	50.105	1.821
Total costs	143.293	146.735	-3.443
Health outcomes			
LYs	3,70	3,55	0,15
HHFs	0,23	0,38	-0,15
QALYs	2,8204	2,7022	0,1182
ICERs			
Total cost per LY	-23.167	DKK/LY	
Total cost per QALY	-29.132	DKK/QALY	

Scenario 4: Mean age 70 years			
	NT-proBNP	**SoC**	**Incremental**
Costs (DKK)			
Diagnostic costs	1.732	439	1.293
HHF costs	10.833	16.001	-5.169
HF ambulatory costs	36.648	35.406	1.242
Total costs	104.059	106.859	-2.800
Health outcomes			
LYs	2,73	2,63	0,10
HHFs	0,16	0,27	-0,11
QALYs	2,0354	1,9556	0,0798
ICERs			
Total cost per LY	-27.353	DKK/LY	
Total cost per QALY	-35.081	DKK/QALY	

Scenario 5: Mean age 80 years			
	NT-proBNP	**SoC**	**Incremental**
Costs (DKK)			
Diagnostic costs	989	248	741
HHF costs	5.007	8.222	-3.215
HF ambulatory costs	16.274	16.654	-381
Total costs	53.596	56.115	-2.520
Health outcomes			
LYs	1,51	1,45	0,06
HHFs	0,07	0,14	-0,07
QALYs	1,0881	1,0435	0,0446
ICERs			
Total cost per LY	-43.303	DKK/LY	
Total cost per QALY	-56.457	DKK/QALY	

5.2.3.3 Two-way Sensitivity Analysis

Table 5.6: *Two-way sensitivity analysis (Age and NT-proBNP cut-off)*

NT-proBNP cut-off		Age 60	66	70	80
≥125 pg/mL	Incremental total cost (DKK)	1.133	801	468	-959
	Incremental QALYs	0,1188	0,0976	0,0801	0,0461
	ICER (Total cost/QALY)	9.536	8.212	5.837	-20.824
≥400 pg/mL	Incremental total cost (DKK)	-3.443	-3.055	-2.800	-2.520
	Incremental QALYs	0,1182	0,0974	0,0798	0,0446
	ICER (Total cost/QALY)	-29.132	-31.359	-35.081	-56.457
>2000 pg/mL	Incremental total cost (DKK)	-14.080	-11.938	-10.238	-5.671
	Incremental QALYs	0,1157	0,0964	0,0784	0,0397
	ICER (Total cost/QALY)	-121.675	-123.832	-130.669	-142.973

To investigate the simultaneous impact of different mean ages and NT-proBNP cut-offs, a two-way deterministic sensitivity analysis was conducted. The results of this analysis are presented in Table 5.6. The columns contain mean ages of 60, 66, 70, and 80 years, while the rows entail NT-proBNP cut-offs of ≥125 pg/mL, ≥400 pg/mL, and >2000 pg/mL. The results presented are the incremental total costs, incremental QALYs, and the ICER (total cost/QALY), in which green cells indicate cost-effectiveness when applying a cost-effectiveness threshold of 260.000 DKK/QALY. The results of the two-way sensitivity analysis indicate that both increased age and NT-proBNP cut-off produce more cost-effective ICERs compared to younger age and lower cut-offs. When looking at the incremental total costs, only an NT-proBNP cut-off ≥125 pg/mL at ages 60, 66, and 70 are associated with additional costs, while the remaining nine scenarios are cost-saving. The amount of costs saved decreases with age but increases with the NT-proBNP cut-off. Thus, the most cost-saving scenario is at a mean age of 60 years and an NT-proBNP cut-off >2000 pg/mL, with an incremental total cost of -12.032 DKK. When looking at the health outcome QALY, the incremental values similarly decrease not only with age but also with the NT-proBNP cut-off. Consequently, an NT-proBNP cut-off ≥125 pg/mL at a mean age of 60 years results in most QALY gained of all 12 scenarios in the matrix, while an NT-proBNP cut-off >2000 pg/mL at a mean age of 80 years results in the lowest health gain. As indicated by the green color, all ICERs are cost-effective when applying a cost-effectiveness threshold of 260.000 DKK/QALY, but the lowest ICER is produced by an NT-proBNP cut-off >2000 pg/mL at a mean age of 80.

6. Discussion

This section will summarize the findings of the study and discuss the structure of the model, as well as how diagnostic accuracy is incorporated into the model framework. Moreover, the assumptions related to the estimation of costs will be discussed, and how these might impact this study's results and interpretations. Finally, the section discusses thee limitations of the study and avenues for further research on screening with NT-proBNP in a T2DM population in an ambulatory care setting.

6.1 Summary of Study Findings

The base case results of the CEA indicate that an annual screening with NT-proBNP at a cut-off value $\geq$400 pg/mL is cost-saving and more effective compared to the SoC strategy when estimating costs and outcomes over a 6-year time horizon. Results of the one-way DSA indicate that the health state costs of 'Advanced HF' and 'HF' had the biggest impact on the ICER. This is followed by the probability of transitioning from 'Advanced HF' to 'Dead' and the probability of developing symptoms of HF. Results of the PSA show a 95,55% probability of the NT-proBNP strategy being cost-effective under the assumed parameter uncertainty when applying a WTP threshold of 260.000 DKK/QALY. Meanwhile, the results of the scenario analysis investigating different NT-proBNP cut-off values indicate that a higher cut-off value produces both lower incremental total costs and health outcomes, yet the ICER is preferable compared to a lower cut-off value. Similarly, the scenario analysis comparing different mean ages for entering the model shows that an increased mean age results in lower incremental total costs and health outcomes, while the ICER becomes increasingly more attractive. These tendencies were also present in the two-way sensitivity analysis, which showed the most advantageous ICERs when applying a high NT-proBNP cut-off value across all mean ages. Application of different NT-proBNP cut-off values and their impact on the ICER rely on how the model is structured and how the diagnostic accuracy is incorporated in the transition probabilities applied in the model.

6.1.1 Model Structure and Incorporation of Diagnostic Accuracy

The model in this study is structured under the assumption that screening with NT-proBNP will result in earlier detection of T2DM patients with HF than with the current diagnostic strategy. As such, the sensitivity of NT-proBNP is incorporated into the transition probability from 'Alive' to 'HF' in the NT-proBNP arm. However, the specificity of NT-proBNP is only applied in the calculation of diagnostic costs associated with the use of NT-proBNP alongside the sensitivity. Meanwhile, the SoC arm of the model is structured under the assumption that only patients exhibiting symptoms of HF are referred for an echocardiography. Common for both diagnostic strategies is the assumption that

echocardiography will confirm all cases of HF among T2DM patients. While this produces some implications (such as underestimation of costs and overestimation of diagnostic accuracy of SoC) when interpreting the model results, these assumptions are made to simplify the patient flow and clinical pathway.

Regarding assumptions associated with the SoC strategy, the clinical assessment of symptoms is an important yet difficult practice, as symptoms of HF are typically non-specific including dyspnea, fatigue, and edema. Especially in the early stages of HF, it becomes difficult to accurately diagnose the disease [1]. Possible symptoms are assessed by healthcare personnel and the assessment is inevitably influenced by variation between assessors. Moreover, the assessment of symptoms of HF does not include the high-risk markers present in patients referred for echocardiography as per guidelines by DCS [5]. This is manifested in the one-way DSA results, which show that the uncertainty related to the probability of developing symptoms of HF has a relatively high impact on the ICER. Moreover, the model does not account for T2DM patients developing these non-specific symptoms which could indicate HF, but also could be caused by other complications. Hereby, the model does not reflect the resource use related to patients referred for echocardiography due to suspicion of HF in which the echocardiography will rule out HF. As such, the 'false positives' are not included in the SoC arm, and hereby the diagnostic costs related to the SoC strategy may be underestimated, consequently leading to underestimation of the cost-effectiveness of the NT-proBNP strategy. Additionally, echocardiography is assumed to be 100% accurate in confirming HF. Similar assumptions have been made in other studies investigating the cost-effectiveness of NT-proBNP compared to clinical assessment and echocardiography [33, 40]. Meanwhile, another study assumed a sensitivity of 92% and a specificity of 96% [41]. These assumptions are products of simplification of the echocardiography which consists of multiple parameters [4]. To more accurately simulate the diagnostic accuracy of the echocardiography, specific parameters and their respective discriminatory values could be selected and applied in the model. However, this would increase the complexity of the model, and such a delimitation could lead to the exclusion of important aspects in the assessment of HF. In sum, the simplification of the SoC strategy may not be representative of the actual accuracy and resource consumption related to this diagnostic approach as assumptions regarding non-specific symptoms, diagnostic accuracy, and false positives.

The model itself is structured based on the assumption that the screening with NT-proBNp will increase the number of patients diagnosed with HF with the aim of earlier treatment and subsequent decreased morbidity and mortality [1]. This dynamic is incorporated in the structure by comparing the sensitivity of NT-proBNP (cut-off $\geq$400 pg/mL) to the probability of developing symptoms of HF which simulates the clinical flow of the SoC strategy. This comparison could presumably result in an increased number of patients diagnosed with HF and subsequently an increased number of HHFs and

deaths in the NT-proBNP arm. However, these consequences would be counterintuitive when looking at the aim of secondary disease prevention which seeks to reduce disease development and mortality by early diagnosis and intervention [28, 29]. It is therefore important to incorporate the mortality and probability of HHF of those who are asymptomatic in the SoC arm and the false negatives in the NT-proBNP arm. In this study, the asymptomatic patients and the false negatives are assumed to have a probability of HHF and death equal to those who are diagnosed with HF. Consequently, the results of the study show that the incremental HF ambulatory costs are at 1.540 DKK while the incremental HHF costs are at -5.922 DKK in the base case analysis (Table 5.1). The additional HF ambulatory costs therefore indicate an increase in patients diagnosed with HF, while the incremental HHF costs indicate fewer HHFs which is substantiated by the health outcome HHF which is at an incremental value of 0,01 per person. These costs and health outcomes are a consequence of the difference in the number of patients undergoing diagnostic evaluations in the two arms of the model. In the NT-proBNP arm, all patients are screened with NT-proBNP, and with a sensitivity of 81,7%, the probability of disease detection is relatively high. Meanwhile, all patients undergo clinical assessment in the SoC arm, however, as only 9,8% develop symptoms of HF, a significantly smaller proportion of HF cases are detected. Hereby, the proportion of asymptomatic HF patients in 'Alive' in the SoC arm is larger than the proportion of false negative HF patients in the NT-proBNP. As these patients have an increased probability of death and HHF than non-HF patients, it will result in more HHFs and deaths in the SoC arm compared to the NT-proBNP arm.

While the increased probability of death and HHF for asymptomatic and false negative patients is implemented in the model, the specific probability estimates might not be accurate when taking disease severity into account. The definition of HF in this study is broad and includes both HFrEF and HFpEF. Moreover, these types of HF are associated with different prognoses and severity [1]. As such, when including all HF patients in this study and applying the same mean probabilities of death and HHF for patients with and without symptoms of HF, it might lead to underestimating the risk of HHF and death for patients with severe HF and overestimate these risks among patients with less severe HF. Meanwhile, the probabilities among asymptomatic patients treated for HF are not accounted for in the model. Thus, while the results reflect some indication that an early intervention will reduce morbidity and mortality, it is completely dependent on the detection and not the impact of early intervention, which is essential for patients with HF. As a result, the benefit of early intervention is underestimated [1]. Similar implications are applicable when looking at the estimated HSUVs, however to a lesser extent. The HSUV for patients in 'Alive' is applied for all patients in the health state regardless of symptoms or false negatives. However, in the NT-proBNP arm, patients diagnosed with HF may not necessarily have developed symptoms impacting their QoL, but in this study, these patients are assumed to have an HSUV equal to those who have symptoms. Consequently, by placing asymptomatic HF patients, in the HF health state we assume a lower utility than what might be the reality, which

could overestimate the NT-proBNP strategy when comparing it to the SoC strategy.

6.1.2 Assumptions Related to Cost Estimation

The cost estimates applied in the model are based on a number of assumptions, which result in a high level of uncertainty implicating the interpretation of the results presented in this study. This might have something to do with the source and characteristics of the data utilized in the model. The costs related to the health states 'Alive' and 'HF', and pharmaceutical treatment of HF is based on the findings of the study by Sortsø et al. (2016), while costs related to the health state 'Advanced HF' are based on the study by Sortsø et al. (2016) and Bundgaard et al. (2019) [3, 48]. As described in Sections 2.1.3 and 4.3.2, the cost estimates reported in the study by Sortsø et al. (2016) include indirect and direct costs, while representing the average costs per person in a Danish T2DM population [3]. Applied in this model are the average secondary healthcare costs and the average pharmaceutical costs per person and the application of both these are associated with issues. Firstly, the secondary healthcare costs are reported for both no, minor, and major complications, of which costs related to no complications are applied for the health state 'Alive' while the costs related to major complications are applied for the health state 'HF'. While HF is included in the study by Sortsø et al. (2016) as a major complication, diagnoses such as kidney transplantation, dialysis, and amputation above ankle level are also included in the classification of major complications. Complications such as these presumably require multiple check-ups and extensive treatment compared to HF. Hence, by assuming that the average annual cost of HF per person is equal to that of major complications reported by Sortsø et al. (2016), the health state cost of 'HF' might be overestimated.

Meanwhile, the cost of HHF is assumed to be equal to the annual cost of HHFs reported by Bundgaard et al. (2019) [48]. In this study, the annual cost of HHF in addition to the secondary healthcare costs related to major complications extracted from Sortsø et al. (2016) is assumed to compose the health state cost of 'Advanced HF'. However, the secondary healthcare cost extracted from Sortsø et al. (2016) may include hospital admissions and hereby there is a possibility of double counting when adding the cost extracted from Bundgaard et al. (2019). This could lead to a possible overestimation of especially the health state cost of 'Advanced HF'. This is an important consideration as the base case results show that the cost component 'HHF costs' constitute a large part of the cost-saving related to the utilization of the NT-proBNP strategy compared to the SoC strategy. The importance of the health state cost of 'Advanced HF' is also highlighted in the one-way DSA in which the uncertainty related to this parameter has the biggest impact on the ICER followed by the health state cost of 'HF'. Due to the consequences of the possible double counting and overestimation of costs related to HF and HHF, the results should be interpreted with caution when looking at the incremental costs and the ICER. However, the model is calibrated with the best available data, from reliable studies reporting the societal and healthcare costs related to T2DM and its complications [3, 48].

6.2 Limitations

The availability of data is an important limitation in this study, as the aim was to simulate and investigate the use of NT-proBNP as a screening marker for HF in the Thousand&2 Cohort [4]. The conceptual model and model framework are based on the population and clinical pathway of the population in the cohort. As discussed previously, the assumptions related to the cost estimates may result in high levels of uncertainty and the data from the cohort could have contributed to more accurately estimating the resource consumption related to the different health states. Consequently, the application of the data of the Thousand&2 Cohort could provide more representative results of a Danish T2DM population in an ambulatory care setting. Moreover, the Thousand&2 Cohort could provide data that could contribute to the estimation of the transition probabilities. In this study, the transition probabilities are based on a range of studies investigating relevant, yet different populations. More importantly, the use of Thousand&2 Cohort data could provide data on the mortality and hospitalization rates of patients receiving early treatment for HF compared to patients receiving later treatment. By implementing such data, the model would also reflect the benefit of earlier detection of HF and hereby a more nuanced and accurate estimation of the benefit of the implementation of a screening strategy with NT-proBNP.

Another limitation associated with the availability of data is the time horizon applied in the study. A 6-year time horizon was applied in this study to include relevant costs and health benefits associated with the different diagnostic approaches. It would be relevant to apply a longer time horizon as both T2DM and HF are chronic conditions affecting the health of the patients throughout life. However, the estimates of the annual transition probabilities applied in the model are based on different incidence, hospitalization, rehospitalization, and mortality rates ranging from 1 to 5 years. When converting the rates to annual probabilities, it was necessary to assume that the event occurred at a constant rate over the time period of the respective rates. While this assumption could be correct, the application of these annual probabilities for longer than the actual time-specific rate might not be accurate. For example, the HHF rate for T2DM patients with HF might increase with increasing age and the current structure of the model does not allow for such a development over time. The only age-dependent probability currently applied in the model is mortality. While the applied transition probabilities related to death are all constant, a baseline probability of dying is applied, reflecting the increase in mortality depending on age. In conclusion, the current study has been calibrated with the best available data to my knowledge, however, data from the Thousand&2 Cohort would provide a more accurate estimation of both costs and effects related to each of the diagnostic strategies.

6.3 Current Knowledge and Further Research

As mentioned previously, NT-proBNP is currently recommended as a rule-out biomarker in the primary care sector and emergency departments in Denmark, for both T2DM and non-T2DM patients [5, 11]. However, studies and international clinical guidelines, suggest that regular assessment of NT-proBNP values among T2DM patients may contribute to early detection of HF, as the biomarker is a reliable rule-out biomarker at different cut-off values in this population [1, 6, 10]. Furthermore, a cost-effectiveness study by Walter et al. (2023), indicates that NT-proBNP-supported screening of HF among T2DM patients is cost-effective compared to clinical assessment and subsequent echocardiography in an Austrian and Swiss setting [40]. These findings are consistent with the results of this current study, which indicate that annual screening with NT-proBNP for HF is both cost-saving and increases health benefits compared to clinical assessment and subsequent echocardiography among T2DM patients in ambulatory care. However, the results of this study should be interpreted with caution due to assumptions regarding the SoC strategy and clinical pathway. Moreover, the availability of accurate and representative data was limited and application of data from the Thousand&2 Cohort would improve the validity of these results. Therefore, it would be relevant to conduct a health economic evaluation based on these data to more accurately estimate the costs and effects related to both diagnostic approaches in a Danish ambulatory care context. Finally, a budget impact analysis (BIA) should be conducted to estimate the economic consequences related to implementing NT-proBNP as a screening marker over a longer period of time. The BIA would provide information to the Danish authorities on the expected changes in the expenditures related to implementing a new screening program in ambulatory care [32].

7. Conclusion

This model-based cost-effectiveness analysis aimed to investigate the use of screening for HF with NT-proBNP (cut-off $\geq$400 pg/mL) among T2DM patients in a Danish ambulatory care setting compared to SoC, including clinical assessment of symptoms and subsequent echocardiography. Based on the findings in the base case analysis, the NT-proBNP strategy is cost-effective compared to the SoC strategy when applying a WTP threshold of 260.000 DKK/QALY. When considering the incremental total costs and QALY, the NT-proBNP strategy is both cost-saving and provides increased health compared to SoC. The DSA indicated that health state costs related to 'Advanced HF' and 'HF' had the greatest impact on the ICER, while the PSA indicated a 95,55% probability that the NT-proBNP strategy is cost-effective when applying a WTP threshold of 260.000 DKK/QALY. Scenario analyses showed that higher cut-off values of NT-proBNP and mean age for entering the model resulted in the NT-proBNP strategy being more cost-effective compared to the SoC strategy. Based on the best available data, the assumptions made in the analysis, and the cost-effectiveness at a WTP threshold of 260.000 DKK/QALY, this study supports the implementation of an annual NT-proBNP screening for HF among T2DM patients in Danish ambulatory care centers.

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A. Appendix: Transition Probabilities

A.1 SoC from 'Alive' to 'HF'

The probability of transitioning from 'Alive' to 'HF' is in the SoC arm based on the annual probability of developing HF among T2DM patients and the probability of showing symptoms of HF when the condition has been developed. When utilizing the inputs displayed in Table 4.1 the calculation for this probability is thus:

$$0,07 \times 0,098 = 0,007$$

A.2 NT-proBNP from 'Alive' to 'HF'

The probability of transitioning from 'Alive' to 'HF' is in the SoC arm based on the annual probability of developing HF among T2DM patients and the sensitivity of NT-proBNP $\geq$400 pg/mL. When utilizing the inputs displayed in Table 4.1 the calculation for this probability is thus:

$$0,07 \times 0,817 = 0,057$$

A.3 'Alive' to 'Advanced HF'

The probability of transitioning from 'Alive' to 'Advanced HF' is based on the 4-year rate for hospitalization for HF in T2DM patients from the study by Cavender et al. (2015) [50]. Firstly, the 4-year rate is converted to a 1-year rate using the formula:

$$Rate = \frac{-ln(1-p)}{t} \tag{A.1}$$

in which p is probability and t is time and the incidence is assumed to be constant over time.
The 1-year rate is converted to a 1-year probability using the formula:

$$Probability = 1 - exp^{(r-t)} \tag{A.2}$$

in which r is rate and t is time.
The calculation of the 1-year probability of hospitalization for HF in T2DM patients without known HF is thus:

$$1 - e^{(-\frac{-ln(1-0,094)}{4} \times 1)} = 0,024$$

A.4 'Alive' to 'Dead'

The probability of transitioning from 'Alive' to 'Dead' is based on a 1-year rate from the study by Barkoudah et al. (2012) [51]. Using the equations A.1 and A.2 the 1-year probability is thus:

$$1 - e^{(-\frac{-ln(1-0,018)}{1} \times 1)} = 0,018$$

A.5 'HF' to 'Advanced HF'

The probability of transitioning from 'HF' to 'Advanced HF' is based on the 4-year OR extracted from Cavender et al. (2015) [50]. Firstly, the 4-year OR is converted to a 4-year rate with the formula:

$$Rate = \frac{OR}{1 + OR} \tag{A.3}$$

When applying the OR from the study by Cavender et al. (2015) the 4-year rate is:

$$\frac{4,72}{1 + 4,72}$$

The formulas A.1 and A.2 is then used to calculate the 1-year probability:

$$1 - e^{(-\frac{-ln(1-0,083)}{4} \times 1)} = 0,353$$

A.6 'HF' to 'Dead'

The probability of transitioning from 'HF' to 'Dead' is based on a 5-year rate from the study by Johansson et al. (2014). Using the formulas A.1 and A.2 the 1-year probability of transitioning from 'HF' to 'Dead' is:

$$1 - e^{(-\frac{-ln(1-0,58)}{5} \times 1)} = 0,159$$

A.7 'Advanced HF' to 'Advanced HF'

The probability of staying in the health state 'Advanced HF' after 1 year is based on the 1-year rate of rehospitalization for HF extracted from the study by Freedman et al. (2022) [53]. Using the formulas A.1 and A.2 the 1-year probability of transitioning from 'Advanced HF' to 'Advanced HF' is:

$$1 - e^{(-\frac{-ln(1-0,25)}{1} \times 1)} = 0,25$$

A.8 'Advanced HF' to 'Dead'

The probability of transitioning from 'Advanced HF' to 'Dead' within 1 year is based on the 1-year mortality rate in patients hospitalized for HF extracted from the study by Freedman et al. (2022) [53]. Using the formulas A.1 and A.2 the 1-year probability of transitioning from 'Advanced HF' to 'Dead' is:

$$1 - e^{(-\frac{-ln(1-0,35)}{1} \times 1)} = 0,35$$

B. Appendix: Health State Utility Values

B.1 Estimation of Health State Utility Values for 'HF'

The multiplicative method presented in the article by Ara et al. (2017) was used to estimate the health state utility values for 'HF' and 'Advanced HF' as patients in these health states suffer from T2DM as the primary condition and HF or Advanced HF as comorbidity [59]. The formula for estimating HSUVs for comorbidities using the multiplicative method is:

$$AB = U\_nAnB \times \frac{U\_A}{U\_nA} \times \frac{U\_B}{U\_nB} \tag{B.1}$$

in which U is utility, AB is both condition A and condition B, nA is not condition A, nB is not condition B, and $nAnB$ is neither condition A nor condition B.

In this calculation condition A is defined as T2DM, while condition B is defined as HF. The study by Hvidberg et al. (2023) reports HSUVs for chronic conditions in a Danish population based on the EQ-5D-3L. The observed mean HSUV for patients with T2DM is 0,752 and this value represents U_A. The observed mean HSUV for patients without chronic disease is reported to be 0,917. In this study, this value is assumed to be applicable to patients without T2DM, U_nA, and patients without HF, U_nB. The reported HSUV for patients with HF is 0,678; in this study, this value represents U_B. The study by Hvidberg et al. reports an HSUV of 0,974 for patients answering 'Excellent' on the SF-13 general health questionnaire [44]. In this study, this HSUV is assumed to be representative of the HSUV patients with neither T2DM nor HF, U_nAnB. When applying these values to formula B.1 it produces an HSUV of the health state 'HF' of:

$$0,974 \times \frac{0,752}{0,917} \times \frac{0,678}{0,917} = 0,5906$$

B.2 Estimation of Health Statue Utility Values for 'Advanced HF'

The HSUV for 'Advanced HF' in this study is based on the HSUV for 'HF' of 0,5906 calculated in the previous section and the HSUV of 0,47 for patients hospitalized for HF reported by Gu et al. (2020) [45]. For this study, the length of an average hospitalization stay is assumed to be 10 days and the calculation for the HSUV for 'Advanced HF' is thus:

$$\frac{0,47}{365,25} \times 10 + \frac{0,5906}{365,25} \times 355,25 = 0,5873$$

C. Appendix: Cost Calculations

C.1 Adjustment for Inflation

To estimate the present value of costs extracted from the literature, they were adjusted for inflation using the formula:

$$Present\ value = \frac{amount \times new\ index}{old\ index} \tag{C.1}$$

Consumer price indexes were extracted from Statistics Denmark and the used indexes are presented in table C.1 [60].

Table C.1: *Consumer price index from Statistics Denmark [60]*

Year	Consumer price index
2016	99,4
2019	102,3
2024	117,8

The adjusted costs are presented in table C.2 with costs in € converted to DKK at an exchange rate of 7,46 (as per 01/01-2024) [61]. The calculations of the present values, using formula C.1 and the indexes in table C.1, are presented in the following subsections.

Table C.2: *Costs adjusted for inflation*

	Cost (€)	Cost (DKK)	Year	Present value (DKK)
Alive	2690	20.063	2016	23.777
HF	9339	69.654	2016	82.548
HHF	7844	58.504	2019	67.368
HF Treatment	595	4.438	2016	5.259

C.1.1 Health State Cost 'Alive'

$$\frac{20.063 \times 117,8}{99,4} = 23.777\ DKK$$

C.1.2 Health State Cost 'HF'

$$\frac{69.654 \times 117,8}{99,4} = 82.548\ DKK$$

C.1.3 Average Cost of Hospitalization for HF

$$\frac{58.504 \times 117,8}{102,3} = 67.368\ DKK$$

C.1.4 Average Cost of HF Treatment

$$\frac{4.438 \times 117,8}{99,4} = 5.259\ DKK$$

C.2 Health State Cost of 'Advanced HF'

The annual cost associated with the health state 'Advanced HF' is based on the annual cost of 'HF' extracted from the study by Sortsø et al. (2016) and the average annual cost of inpatient admissions for patients with HF extracted from the study by Bundgaard et al. (2019) [3, 48]. Bundgaard et al. (2019) report an average annual cost of inpatient admissions for patients with HF of 7.844€ [48]. This is added to the secondary healthcare cost per person-year of T2DM patients with major complications of 9.339€ [3]. When using the adjusted costs from the previous section, the annual cost of the health state 'Advanced HF' is thus:

$$67.368 + 82.548 = 149.916\ DKK$$

D. Appendix: Tornado plot

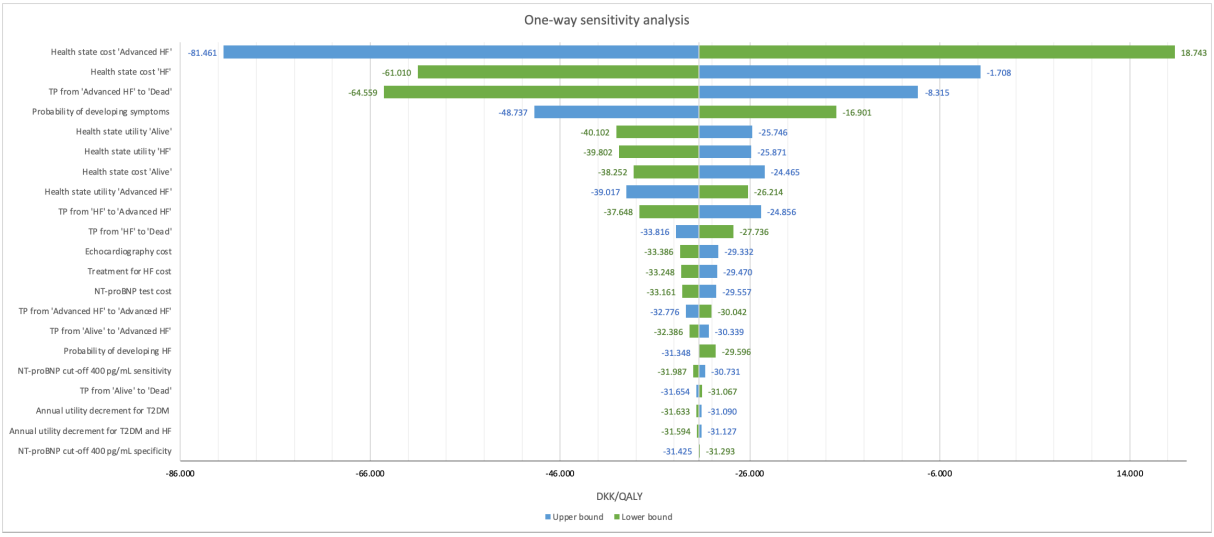

Figure D.1: *Tornado plot depicting the one-way sensitivity analysis*