Health Economic Evaluation of Screening with NT-proBNP for Heart Failure in Patients with Type 2 Diabetes

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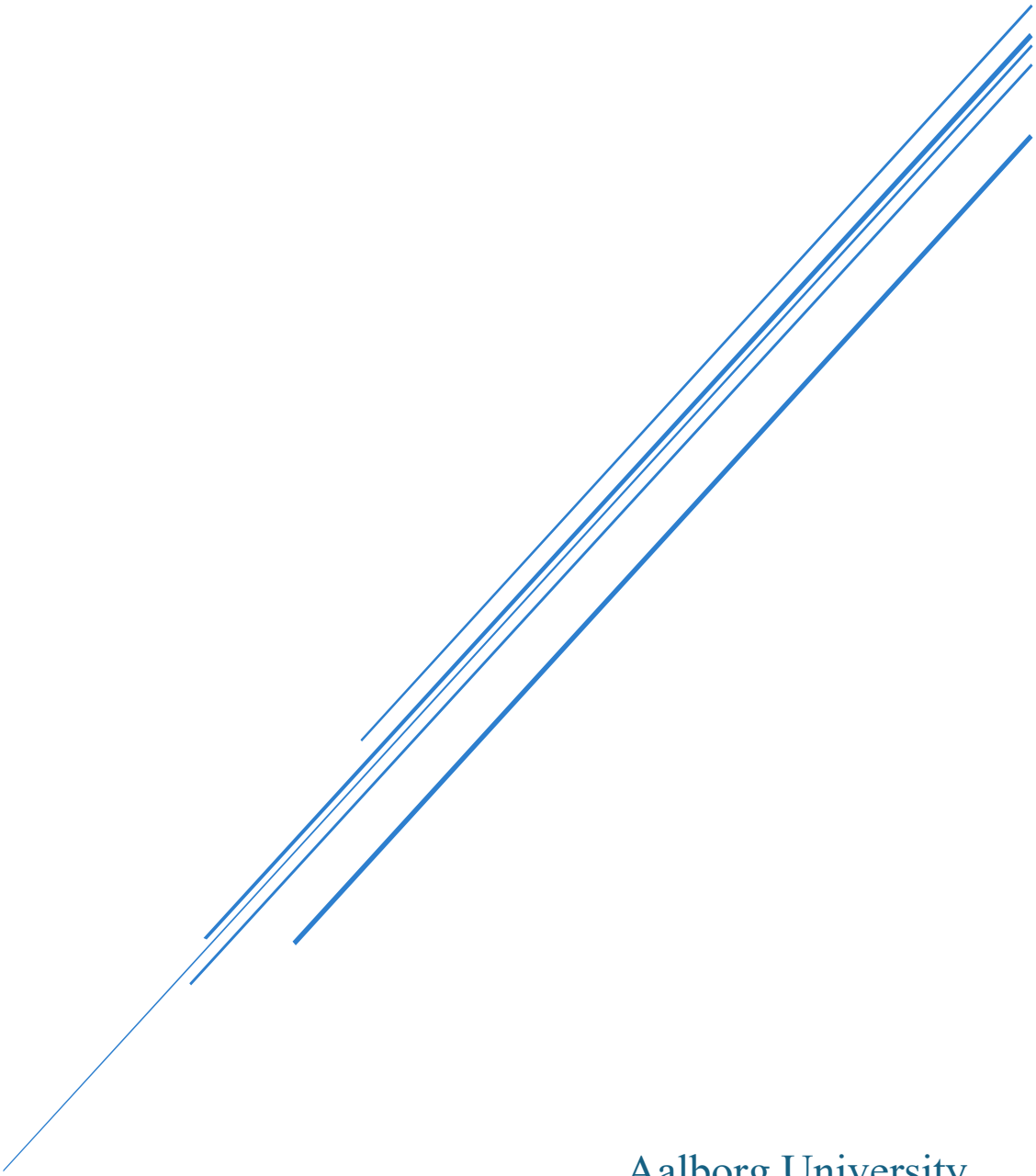

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STUDENT REPORT

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Preface:

The original group members of this master thesis were Patrick Nasehi Jacobsen (Study number 20193675) and Augusta Munster Spanger Ries (Study number: 20193683). The group decided to split, which took place on the 15th of May 2024. Aalborg University states that after a group has decided to split up, the project members need to highlight in the preface what has been done before the date for the decision to split the group.

The following was done before the 15th of May 2024: Within the background section, the writing about Type 2 Diabetes Mellitus, Heart failure and Risk Factors, SGLT2i inhibitors, Economic burden of Type 2 Diabetes mellitus and heart failure, Predicting and Diagnosing heart failure in type diabetes, Echocardiography, natriuretic peptides, NT-proBNP and current guidelines, in this order. The order has now been changed to what can be seen in this analysis. All the subsections have been edited to create a flow through the background section. Also, a few sources have been added as an extra throughout the background section, yet a lot of text remains the same. The current research section, subsection: literature search, is the only part of the current research section written before the 15th of May. The rest has been written after the date. The aim remains the same before the date but has been moved to the introduction section after the stated date. Within methods, the following was done before the date: Model framework, health states, model input, transition probabilities, health state cost, meta-analysis, and sensitivity analysis. It's worth highlighting that after the date, the model framework has been changed and added with information; the same goes for costs for the health state. The utility section remains primarily the same. Meta-analysis within the method section has been changed. The model, created in Excel, remains the same and hasn't been changed, and the same goes for the results sections. However, all the text within the result section has been added after the date, except for the forest plot and one-way sensitivity analysis. The rest of the master thesis has been produced after the 15th of May 2024.

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Abstract

Background: T2DM is a chronic disease in which the body can't sufficiently produce insulin, which can lead to increased blood glucose levels. In Denmark around 322.000 Danes are living with T2DM, with around 100.000 undiscovered cases. T2DM deals with a lot of comorbidities, and the most frequent cardiovascular comorbidity is HF. T2DM with HF has an increased risk of getting hospitalized and an increased mortality rate. The most efficient way to diagnose HF is via echocardiography. However, the Danish guidelines recommend using the plasma marker NT-proBNP as a rule-out for HF to improve the diagnostic workup. NT-proBNP could potentially avoid the unnecessary use of echocardiography. The Danish guidelines also state that the most efficient treatment of T2DM patients with HF is the incorporation of SGLT2i. This treatment has been shown to reduce hospitalizations within T2DM patients with HF and their mortality rate. By reducing these factors, the NT-proBNP might benefit the Danish healthcare system by reducing the costs associated with T2DM and HF and helping the diagnostic.

Aim: This master's thesis aims to investigate the cost-effectiveness of annual screening with NT-proBNP and additional treatment with SGLT2i compared to current diagnostic practice and treatment of HF in T2DM patients in a Danish ambulatory care setting.

Methods: A Markov model was utilized to estimate cost and QALY for screening T2DM ambulatory patients for HF, with a hypothetical population of 1,000 patients at NT-proBNP cut-off value at ≥ 400 pg/mL. A limited sociological perspective was utilized. The Markov model uses a five-year time frame with a one-year cycle length. A meta-analysis was conducted to extract treatment values. Base case results, one-way deterministic sensitivity analysis, and scenario analysis were calculated.

Results: Base-case results show that the incremental cost between the NT-proBNP+SGLT2i arm and the SoC arm is 1.503 DKK, with an ICER of 63.400 DKK/QALY. The NT-proBNP arm shows a lower HHF compared to SoC. The one-way DSA shows the most uncertainty regarding HF hospitalizations. The scenario analysis shows that a cut-off ≥ 125 pg/mL has a higher incremental cost and ICER than SoC but remains cost-effective, with an ICER of 171.025. The cut-off ≥ 2000 pg/mL shows a dominant easier, making it cheaper and more effective, with an ICER of -147.507 DKK /QALY.

Conclusion: This Markov model-based health economic evaluation shows that using an NT-proBNP cut-off value at ≥ 400 pg/mL NT-proBNP + SGLT2i compared to SoC, makes NT-proBNP+SGLT2i cost-effective when utilizing the NICE-recommended WTP threshold.

Abbreviations

ASCVD	Atherosclerotic Cardiovascular Disease
BNP	Brain natriuretic peptide
CfD	Center for Diabetes Research
CEA	Cost-effectiveness Analysis
CI	Confidence Interval
CUA	Cost-Utility Analysis
CVD	Cardiovascular Disease
DCS	Dansk Cardiologisk Selskab
DKK	Danish Krones
DM	Diabetes Mellitus
DRG	Diagnosis-related-group
DSA	Deterministic Sensitivity Analysis
ECG	Electrocardiogram
FE-model	Fixed-effect model
HHE	Health Economic Evaluation
HF	Heart Failure
HHF	Hospitalization due to Heart Failure
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HSUV	Health State utility values
ICER	Incremental Cost Effectiveness Ratio
MACE	Major Adverse Cardiovascular Events
MLHFQ	Minnesota living with heart failure questionnaire
NP	Natriuretic Peptides
NT-proBNP	N-terminal pro-b-type natriuretic peptide
PICO	Population, Intervention, Comparator, Outcome
pg/mL	Picogram/milliliter
PRISMA	Preferred Reporting Items for Systematic review and meta-analyses
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-adjusted Life year
SDC	Steno Diabetes Center
SF-12	Short Form - 12
SF-36	Short Form – 36
SGLT2i	Sodium-glucose cotransporter-2 inhibitor
SoC	Standard of Care
Symp.	Symptoms
T2DM	Type 2 Diabetes Mellitus
WTP	Willingness-to-Pay.

Table of Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) is a chronic disease/condition that is the primary type of diabetes mellitus (DM) overall. It is characterized as a condition that doesn't utilize insulin properly, which creates imbalances in the patient's blood sugar levels [1], [2], [3], [4].

In Denmark, T2DM is a considerable burden on Danish society and is a chronic condition that increases the number of cases each year. Around 322.000 people in Denmark are diagnosed with T2DM, and 100.000 people are estimated to be undiscovered with T2DM. 88 % of the total number of T2DM cases in Denmark are treated in the primary care sector, while the remaining 12 % are referred to specialized clinics due to a worsening state of their T2DM [5].

When T2DM patients are treated, the primary objective is to obtain stable blood glucose levels. Achieving this will help reduce the comorbidities associated with T2DM. Usually, T2DM patients have more than one comorbidity, where 40 % of these are due to cardiovascular disease (CVD)[5]. The usual CVD present in T2DM patients is Heart failure (HF). HF is seen in up to one-third of the T2DM population and is very prominent among the elderly. Also, T2DM with HF has a 33 % increase in hospitalization due to heart failure (HHF) [3]. HF is an umbrella term that is not categorized as a single disease but a syndrome. HF is diagnosed in 66.000 people in Denmark, with around 9.000 new cases yearly [3], [6].

The syndrome is usually seen with symptoms such as shortness of breath, fatigue, and edema. HF cases are also seen with heart structure and function changes, diagnosed by echocardiography[3]. When dealing with HF, the diagnostic workup is a crucial part of the final diagnosis to find the cause and severity of HF. If the clinicians detect HF in T2DM patients, they start treatment and get referred to specialized clinics [7]. However, to support the diagnostic workup of HF, the plasma marker NT-proBNP is recommended within the Danish guidelines [8]. NT-proBNP has been recommended as a rule-out diagnostic plasma marker for HF at a cut-off of < 125 pg/mL [8]. It's important to note that these guidelines in Denmark are recommended for HF regardless of T2DM status.[8].

When treating T2DM with HF, the primary medication is Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) [9]. SGLT2i has been shown to reduce HHF and decrease mortality rates [9] and can lower the levels of NT-proBNP in patients with T2DM [3].

Diabetes alone is a substantial economic burden in Denmark, costing society around 32 billion Danish Krones (DKK). Most of the expenses are due to productivity loss [10]. Also, HF creates a

huge economic burden, with around 127.000 DKK for the annual direct cost per HF patient [11]. So, incorporating the plasma marker NT-proBNP as a screening and diagnostic tool in the diagnostic workup for T2DM with HF may reduce HHF and unnecessary echocardiography [6].

This master's thesis aims to investigate the cost-effectiveness of annual screening with NT-proBNP and additional treatment with SGLT2i compared to current diagnostic practice and treatment of HF in T2DM patients in a Danish ambulatory care setting. The cost-effectiveness will be estimated through a Markov model. Data from the literature will form the basis of the current diagnostic practice of HF in Danish ambulatory care and predictive values of NT-proBNP and echocardiography in this specific population. The effect of SGLT2i in T2DM patients with HF will be identified through a systematic literature search and subsequent meta-analysis. The impact of the uncertainty of NT-proBNP diagnostic accuracy on cost-effectiveness will be examined through a deterministic sensitivity analysis and scenario analysis.

2. Background

2.1 Type 2 Diabetes Mellitus and Risk of Heart Failure

2.1.1 Type 2 Diabetes Mellitus

T2DM is the leading type of DM. T2DM is categorized as a chronic disease/condition characterized by the body not efficiently utilizing insulin. When blood sugar levels rise, insulin decreases these blood sugar levels. However, when dealing with T2DM, the pancreas (the primary organ within DM), which produces insulin, is not efficient in reducing blood sugar levels and will lead to prominent damage to the body [1], [2], [3],[4].

The amount of people with T2DM in Denmark is increasing, and a report from 2023 by the Danish Diabetes Association estimated that around 322.000 people in Denmark were living with T2DM. Meanwhile, Steno Diabetes Center (SDC) estimated in 2011 that around 100.000 people in were living with undiscovered T2DM [5]. About 88% of the estimated 322.000 individuals get treated in primary care settings. The remaining 12 % are referred to specialized centers like SDC due to worsening T2DM status. Despite the treatment site, the primary objective in managing T2DM, within Danish guidelines, is to achieve stable and low long-term blood sugar levels [5].

The reason for achieving steady blood sugar levels is that comorbidities associated with T2DM are primarily due to the increase in these blood sugar levels. The comorbidities that will usually be presented in T2DM ambulatory patients are CVD. In Denmark, around 72 % of all T2DM patients have one or more comorbidities, and 40 % of all comorbidities are CVD [5] CVD alone accounts for half of all deaths in this population [12].

The enhanced risk of CVD within T2DM patients is recognized, and various factors, such as blood sugar levels, blood pressure, and kidney function, are the usual factors. It is, therefore, important to measure these values in a timely manner. [13].

One of the primary CVDs that present itself in T2DM ambulatory patients is Heart Failure (HF). In broad terms, clinically manifested HF is seen in about 10-30 % of T2DM patients, especially the elderly population, 70 years or older. T2DM patients are also seen to have a 33 % increase in HHF [3].

2.1.2 Heart failure and Risk Factors

HF is not categorized as one pathological disease but is more often seen as an umbrella term or syndrome. In Denmark, it was estimated that around 66.000 Danes were diagnosed with HF back in 2017. However, the number of cases may be higher since HF is a syndrome that usually goes undiagnosed in people over the age of 60. To this day, every year, around 9.000 newly diagnosed cases with HF occur in Denmark [6].

HF is characterized by various symptoms and changes in the structure or function of the heart [9]. It is a syndrome exhibiting common symptoms like fatigue, shortness of breath, and edema. Changes within the structure and functions of the heart are identified through echocardiography, which is the primary diagnostic method to diagnose HF clinically [3]. HF usually comes from various CVDs and their associated complications, yet research indicates that T2DM independently heightens the risk of HF [14].

According to the European Society of Cardiology (ESC) guidelines, HF can be classified/categorized into three primary disease categories, depending on the ejection fraction (EF) [3], [15]; the ejection fraction is defined as how much of a fraction, the left ventricle of the heart is able to pump out blood. The disease categories are HF with reduced EF (HFrEF < 40 %), HF with preserved EF (HFpEF ≥ 50 %), and HF with mildly reduced EF (HFmEF 41-49 %) [3].

Individuals with T2DM face a higher risk of developing HF. While the precise reasons for the development of HF in T2DM patients remain unclear, multiple risk factors contribute to its development [16].

When dealing with HF, it's fundamental to include the diagnostic workup to assess the etiology and severity of HF and determine whether medication treatment should be incorporated.

The diagnostic workup includes clinician evaluations and echocardiography. When HF is detected, immediate treatment is initiated, and the T2DM patients are referred to clinics specialized in HF [7]. Initially, multiple examinations are performed within the diagnostic workup; these include medical history, which focuses on the cardiac causes of HF and the common symptoms; echocardiography, laboratory tests, and NT-proBNP, which is only recommended when the clinicians are unclear of the clinical picture [7], [17].

The treatment and management of HF require focusing on the overall CVD risks by controlling blood pressure levels, incorporating lifestyle changes, and maintaining optimal blood glucose levels [3]. However, medications that are antidiabetic, known as sodium-glucose co-transporter 2 inhibitors (SGLT2i), have been shown to decrease CVD complications. These medications work by

inhibiting the sodium-glucose cotransporter in the kidneys, reducing glucose reabsorption. This has been shown to decrease the mortality rate and the number of HHF in patients with T2DM and HF [3]. Before going more in-depth regarding the recommendations for diagnosing and screening HF patients and the treatment aspect, it's crucial to understand the basics of echocardiography and NT-proBNP.

2.1.3 Echocardiography

Echocardiography is the primary diagnostic tool for the diagnosis of HF. It is important for healthcare professionals to detect HF and CVD in a timely manner. Echocardiography utilizes ultrasound frequencies to look at the heart structure and function by creating an image through the frequencies. Echocardiography is especially good in patients presenting elevated levels of brain natriuretic peptide BNP or NT-proBNP [18]. The Dansk Cardiologisk Selskab (DCS) position paper recommends that all patients with clinical signs suggestive of HF undergo echocardiography, especially when high-risk clinical markers supplement these signs. The high-risk markers are defined as cardiac dysfunction within medical history, clinical, electrocardiogram (ECG) abnormalities, and imaging [8]. The clinical high-risk markers can be seen in Table 1. In situations where these four clinical high-risk markers are insufficient to diagnose HF, but the clinicians still suspect HF, NT-proBNP measurements may be a diagnostic plasma marker to utilize and more likely rule out HF [9].

Table 1: Four Clinical High-risk Markers of Cardiac Dysfunction [8]

Medical History	Clinical	ECG abnormalities	Imaging
AMI	Killip class II	Atrial Fibrilation	Chest x-ray showing pleural effusion/cardiac decompensation
Dysregulated Hypertension	Orthopnea	Frequent Q-waves	
Diabetes	5 kg weightgain within few weeks	LBBB	Lung ultrasound with B lines
		ST-T abnormality	
	Heart murmur		

2.1.4 Natriuretic Peptides

The DCS recommends the utilization of plasma markers, such as natriuretic peptides (NP), in the diagnostic workup of HF in primary care and recommends BNP and NT-proBNP when assessing patients with suspected HF without high-risk markers [8]. BNP is synthesized in the left ventricle. An overload of pressure and ventricle expansion induces this. This will cause cardiac stress, resulting in the synthesis of the prehormone, proBNP, from the heart's muscle cells. This proBNP will then transfer over to the other parts of the heart tissue and be split into the BNP and NT-proBNP[3],[19].

NT-proBNP is cleared through the kidneys, while BNP is removed from plasma, which creates a longer half-life for NT-proBNP. This makes NT-proBNP much more stable plasma markers and creates a better diagnostic marker for HF patients[20],[19], [21].

2.1.5 NT-proBNP and Current Guidelines

HF can lead to elevated levels of NT-proBNP, and the diagnostic plasma marker is recommended by DCS positions paper in the diagnosis of suspected HF in primary care[8], [15], [19]. The DCS position paper on BNP in HF recommends 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 recommended rule-out test for HF at ≤ 125 pg/ml cut-off in patients aged <75 years [8].

The DCS position paper describes that the ≤ 125 pg/ml cut-off value has a high sensitivity and low specificity for HF, which results in many false positive results[8]. A systematic review from 2018, which the DCS-position paper refers to, found that the cut-off ≤ 125 pg/ml has a sensitivity ranging from 88 % to 100 %, while the specificity is low at 49 %[22]. The DCS position paper proposes a ≥ 450 pg/ml cut-off for high-risk HF among patients < 50 years and a ≤ 900 pg/ml cut-off in patients 50-74 years. According to the DCS position paper, an NT-proBNP concentration of ≤ 125 pg/ml is a cut-off value to rule out the diagnosis of HF. Meanwhile, a concentration of ≥ 450 pg/ml indicates a high risk of HF, and patients should then be referred for an echocardiography[8]. These recommendations are appropriate for patients suspected of HF regardless of T2DM as DCS treatment guidelines for diabetes and cardiovascular disease refer to the DCS position paper regarding NT-proBNP and BNP in HF [9].

It is also important to consider the more international guidelines regarding using NT-proBNP as a diagnostic plasma marker for HF. A study by Taylor et al. (2023) looked at the diagnostic performance of utilizing NT-proBNP at different cut-offs to get a referral for echocardiography. The study analyzed the ESC cut-off of NT-proBNP at ≥ 125 pg/mL and a NICE cut-off at≥ 400 pg/mL

within primary care. The study shows the diagnostic accuracy of HF using NT-proBNP by calculating both sensitivity and specificity at different cut-offs. They concluded that utilizing a higher NT-proBNP cut-off, only 20 % of the HF cases are missing in primary care. However, when dealing with a lower cut-off, ≥ 125 pg/mL, there is a need for more diagnostic accuracy to diagnose HF [23].

However, studies show that in addition to the diagnostic value of HF, NT-proBNP has a predictive value for identifying T2DM patients at risk for developing HF [24], [25], [26]. A prospective cohort study by Busch et al. (2020) investigated the predictive value of different diagnostic tests and whether they could improve lowering the risk of future CVD events in T2DM patients[25]. This study was part of the Thousand&2 study, which recruited T2DM ambulatory patients from SDC and Center for Diabetes Research (CfD), Department of Medicine, Herlev and Gentofte Hospital, University of Copenhagen [27]. The study by Busch et al. (2020) compared NT-proBNP, echocardiography, electrocardiogram (ECG), and albuminuria, among others, in their risk prediction of CVD events. While all the abovementioned risk markers were significantly associated with the CVD, only NT-proBNP (>150 pg/ml) were significantly associated when adjusted for both clinical markers (age, sex, BMI, diabetes duration, systolic blood pressure, and prior CVD) and all four risk markers[25]. This highlights the predictive value of NT-proBNP might have for HF.

2.2 Recommendations for Diagnosing and Screening Heart Failure in Type 2 Diabetes Patients

Before diving more in-depth into the specifics regarding treating T2DM patients with HF, it's important to establish a broad guideline/recommendation for diagnosing and screening HF in T2DM patients [8]. As mentioned above, the diagnosis is primarily done by echocardiography since it’s the most noninvasive method for analyzing the structural changes the heart has developed [3]. Echocardiography should be utilized on all T2DM patients when the clinician suspects HF and when this suspicion is supported by the four clinical high-risk markers [8]. It is also recommended that T2DM patients inquire annually about CVD symptoms, focusing on dyspnea and be cautious about blood pressure [9].

When T2DM patients are advised to undergo echocardiography, supported by these four high-risk markers, the measurement of NT-proBNP is unnecessary in such cases because the patients will be directly referred to get an echocardiography. However, when these four clinical high-risk markers

for HF are absent, the clinicians suspect HF; NT-proBNP has been proven to be a useful diagnostic tool to effectively rule out HF or support further examination with echocardiography [8],[9].
When looking at the DCS position paper regarding their Danish guidelines, they do coincide with the ESC and American Heart Association (AHA) guidelines. The ESC and AHA guidelines state that NT-proBNP can be used to support the diagnosis of HF. This is done by suggesting cut-off values for NT-proBNP at ≥ 125 pg/mL for T2DM patients [3].
As stated in the current background section of this analysis, when HF is detected, immediate treatment will be launched, and the T2DM patients will be referred to specialized clinics [7].

2.2.1 SGLT2 Inhibitors

The DCS guidelines for treating T2DM patients with HF recommend initiating treatment with SGLT2i. SGLT2i (canagliflozin, dapagliflozin, and empagliflozin; the drugs available on the Danish market) demonstrate promising outcomes by reducing HHF and decreasing mortality rates [9]. Selective SGLT2i enhances the elimination of glucose in the kidneys by inhibiting glucose reabsorption. This prevents the usual complete reabsorption of glucose filtered in pre-urine individuals without diabetes [28], [29]. SGLT2i is the first selection of glucose-lowering medications in Denmark, independent of blood glucose levels, for T2DM and HF patients [9].
In Denmark, 66 % of T2DM patients are treated with antidiabetic drugs, not insulin, but metformin, DPP-4 inhibitors, SGLT2i and GLP-1. Within the Danish T2DM population, 5 % take insulin multiple times daily, while 10 % take basal insulin. The remaining 19 % are exclusively treated with diet changes [5]. Over the past few years, there has been a prominent utilization within SGLT2i, and it has quickly become a part of the T2DM patient treatment [5], with the indication of treatment of symptomatic HF both in patients with and without T2DM [28]. By 2022, approximately 28% of all T2DM patients in Denmark were treated with SGLT2i. It is important to note that at the same time, there has been a decline in the amount of T2DM patients utilizing another form of antidiabetic medication, such as insulin [5].
For T2DM patients HF, there is evidence that treatment with SGLT2i reduces mortality and HHF [3], [9]. Therefore, an SLGT2i treatment is initiated independently of the T2DM patient's blood glucose levels [9]. The Danish guidelines correlate with the ESC guidelines in that SGLT2i is the preferred treatment for CVD, regardless of blood glucose levels and other uses of antidiabetic medications [8], [15]. Regarding NT-proBNP, trials have shown a reduction in CVD events among

T2DM patients due to lowered NT-proBNP levels among the T2DM patients who received an SGLT2i. Trials have also shown that SGLT2i can lower NT-proBNP levels in T2DM patients compared to T2DM patients who received standard-of-care treatment [3].

2.3 Economic Burden of Type 2 Diabetes Mellitus and Heart Failure

Diabetes creates a financial burden of at least 32 billion Danish Kroner on the Danish healthcare system each year. Most expenses are due to productivity loss, which amounts to over 13 billion DKK [10]. A study by Sortsø et al. (2016) provided information about the expenses incurred by patients with DM, both with and without complications, in contrast to those without DM, using data they extracted from national registries [10]. The study categorizes patients based on their complications' progression into “no-”, “minor-”, and “major-complications”. Sortsø et al. (2016) consider HF as a major complication. This is important since the study found that DM patients with major complications accumulate many expenses. The study shows that the major complications are the highest considering the total healthcare costs per person-year [10].

However, HF also deals with the high costs associated with the syndrome. In Denmark alone, HF consumed around 2 % of all health expenditures in 2012 [6]. A study by Bundgaard et al. (2019) looked at the economic burden of HF within Denmark from 1998-2016. The study looked at both the direct and indirect costs associated with HF. They showed that 127.000 DKK was the annual direct cost for a single HF patient, while the indirect cost amounted to around 39.000 DKK annually [11]. The direct cost of the study by Bundgaard et al. (2019) included hospitalization due to HF. HF alone in Denmark causes up to 2 % of all hospitalizations in Denmark, which is the reason for such a high annual direct cost for HF patients [11]. In Denmark, around 22.000 hospitalizations are due to heart failure, where 6.000 of them cause re-hospitalization [6]. The study by Bundgaard et al. (2019) showed that it is evident that hospitalization is the reason for such high costs associated with HF and accounts for around 66 % of all the direct costs [11].

Considering all these recommendations and guidelines in Denmark and Internationally, it's prominent that Denmark does not have a precise strategy for screening and diagnosing HF. However, echocardiography seems to be the most precise tool for diagnosing HF, and NT-proBNP is a plasma marker that can help the screening and diagnosis but also, more importantly, help guide the overall diagnostic pathway and timely treatment to avoid unnecessary echocardiography within the Danish healthcare system [6].

3. Current Research

Based on the background chapter, the analysis wants to conduct a literature search. The literature search aims to explore studies on the utilization of NT-proBNP in T2DM patients with HF. The section wants to highlight gaps in the health economic evaluation (HEE) literature and review the methods utilized, population and patient setting, intervention, and cost-effectiveness.

3.1 Literature Search

A literature search was conducted in PubMed to identify the current research on the cost-effectiveness of using NT-proBNP in HF patients. The Population, Intervention, Comparison, Outcome (PICO) model was utilized to identify the search terms. To confirm a search broad enough to include all relevant studies, the Comparison aspect of the PICO model was excluded (Table 2). Population, Intervention, and Outcome are all defined in PubMed mesh terms, as well as title and abstracts (using the command 'Tiab' within PubMed), to include many available studies. The PICO model helped develop the search string by using specific search terms (Appendix A shows the search string)

Table 2: Current Research PICO Model

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 resulted in 149 hits (153 including duplicates, which were removed before screening). These studies were screened by title, abstract, and full-text reading, as displayed in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flowchart [30]. Figure 1 shows the evaluation of the full-text articles based on the inclusion and exclusion criteria, which can be seen in Table 3. The literature search resulted in nine studies that examined the cost-effectiveness or cost-utility of utilizing either NT-proBNP or BNP in screening and diagnosing the different categorizations of HF. The nine studies included in the current research section can be seen in Table 4.

Table 3: Inclusion and Exclusion criteria

Inclusion critetia	Exclusion Criteria
Health Economic Evaluation	Editorials
Elderly Population	Case reports
Model based cost-effectiveness analysis	Acute Dyspnea
or cost-utility analysis	Device therapy
Health technology assessment	Treatment Guidelines
Decision modelling	
Naturetic Peptides	
NT-proBNP	
Heart Failure	

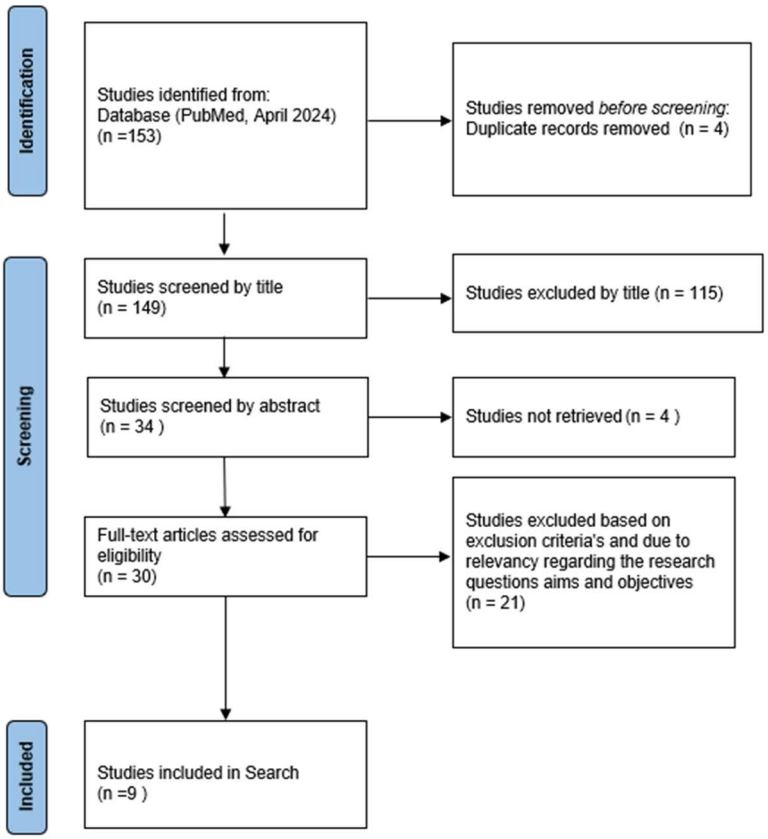

Figure 1: PRISMA-flowchart visualizing the identification, screening, and number of included studies in the current research.

3.1.1 Population and Intervention

When comparing the nine different studies, it is obvious that the studies that provided an estimated age for their population are mainly elderly people. The studies Walter et al. (2023)[31], Siebert et al. (2021)[32], Mohiuddin et al. (2016)[33], Morimoto et al. (2004)[34], and Heidenreich et al. (2004)[35] All included an elderly population, with patients, aged from <50 years to around >75 years. The rest of the studies do not specify the mean age for the population included in their study. Having an older population aligns with DCS positions paper for different age groups for specific

NT-proBNP cut-off values [8].

What is also visible from the studies is that over half of them use a hypothetical population [31], [33], [34], [35], [36], while the rest of the studies either extract the data from a trial cohort [32], [37], [38] or creates a systematic review [39] as well as different settings within all the studies. All the studies have a population that considers a categorization of HF, whereas the only study that hasn't specified which type of HF was considered is Jafari et al. (2018)[39]. What is prominent to note is that the current analysis considers both T2DM patients and HF within the population setting, and only one study was found in the current research which also considers this. The study by Walter et al. (2023) only considers NT-proBNP as a screening tool for HF, compared to having no screening tool, where patients are either presented with or without T2DM [31]. Most of the studies do not specify the patient settings within their population. However, studies like Walkley et al. (2023)[36], Siebert et al. (2021)[32], Pufulete et al. (2017)[37], and Morimoto et al. (2004)[34] report settings like the emergency department, primary and secondary care, and outpatient care, respectively. When considering the intervention utilized in the studies, five of the included studies make use of the NT-proBNP in their HEE [31], [32], [36], [38], [39]. The rest of the studies utilize BNP [33], [34], [35], [37]. This is due to the abovementioned PICO model and search string. Because mesh terms such as BNP and natriuretic peptide have been incorporated, studies utilizing these biomarkers will likely be included in the literature search.

3.1.2 Utilized Methods

Important aspects of the methodology must be considered when developing a HEE. This includes which type of HHE and model to utilize, the inputs needed for the model, the time horizon, and the perspective. When comparing the different studies on their outcome measures, all are cost-effectiveness analyses (CEA), except for Moertl et al. (2013)[38], which is a cost-utility analysis (CUA). Most studies also use QALY and cost as the primary effect measure. However, only the study by Siebert et al. (2021) utilized severe adverse events as the effect measure[32].

When considering the modeling type, most studies utilize a Markov model. However, the studies by Siebert et al. (2021) [32] and Heidenreich et al. (2004) [35] make use of a decision tree model. It is also important to note that the studies utilizing a Markov model all incorporate a time horizon, either a lifetime or Moertl et al. (2013) [38], which uses a 20-year time horizon. This is probably

due to the disease area of HF and T2DM itself, which is categorized as a chronic or lifelong condition [3].

3.1.3 Cost-effectiveness:

All the studies included in the current research report, whether NT-proBNP or BNP, are cost-effective. Walkey et al. (2023) concluded that NT-proBNP is cost-effective when utilizing an age-specific threshold. When utilizing this age-specific threshold, Walkey et al. (2023) state that with minimal loss in sensitivity regarding NT-proBNP, unnecessary echocardiograms can be avoided [36]. Walter et al. (2023) also found NT-proBNP to be a cost-effective diagnostic plasma marker for HF patients, both with and without T2DM, when compared to clinicians only creating a diagnosis based on symptoms [31]. The study by Siebert et al. (2021) supports the Walkey et al. (2023) [36] findings by showing that NT-proBNP is cost-effective when utilized as a supported measurement to create a more accurate HF diagnosis, which could result in fewer HHF and avoid unnecessary echocardiograms [32]. Pufulete et al. (2017) and Jafari et al. (2018) are both a systematic review, and both concluded that NT-proBNP is cost-effective across the board [37], [39]. However, Jafari et al. (2018) stated that utilizing utility values from literature did create an under – or overestimation of QALY [39]. Moertl et al. (2013) found that NT-proBNP is cost-effective when comparing different treatment management and has the possibility of reducing both mortality and HHF [38]. Morimoto et al. (2004) analyzed the plasma marker BNP and concluded that doing BNP measurements regularly could improve QALY and reduce the annual cost relating to HF [34]. Heidenreich et al. (2004), who also used BNP, concluded that using BNP as a screening tool for patients who are asymptomatic and then followed echocardiography compared to those who got abnormal echocardiography did provide higher costs but improved the QALY, to create an acceptable QALY gain cost [35]. Lastly, Mohiuddin et al. (2016) concluded that by using BNP-guided care for HF in younger patients is cost-effective but cannot create a conclusion regarding hospitalization [33].

3.2 Summary of the Literature Search

Based on the studies included in the literature search, the Markov Model is the preferred model to incorporate in a health economic evaluation. The most used effect measure is cost and QALY. Also, the studies consider mostly hypothetical elderly populations within different patient settings. The current research shows a lack of literature on using NT-proBNP as a screening tool for HF in T2DM

patients. Walter et al. (2023) [31] is the only study considering T2DM in their model. It is, therefore, necessary to investigate this area further since T2DM ambulatory patients are at higher risk of CVD[9]. Regarding cost-effectiveness, the studies included in the current research state that NT-proBNP for HF patients is a cost-effective screening and/or diagnostic tool. The studies also state that NT-proBNP can create a more accurate diagnosis, reducing unnecessary echocardiograms and potentially positively impacting the patient's quality of life. However, it's important to note that most of these studies do not represent an ambulatory care setting and don't have an isolated focus on T2DM patients. It is prominent that there is a lack of investigation concerning NT-proBNP and its use within T2DM patients in a Danish or ambulatory setting.

Table 4: Overview of the included articles within the current research

Author (year)	Population and setting	Countries	Intervention vs. comparator	Model type	Horizon and perspective	Outcomes
Walkley et al. (2023) [36]	Patients presenting in EDs with suspected acute HF (hypothetical)	UK	NT-proBNP rule-in/rule-out strategy vs. an NT-proBNP Ro strategy and clinical decision alone	Hybrid decision tree/semi-Markov model	Lifetime horizon Healthcare payer perspective	Costs and QALY
Walter et al. (2023) [31]	Patients ≥60 years with/without T2DM, CHF (hypothetical)	Austria, Switzerland	Screening program of HF using NT-proBNP, compared with no screening	Time-discrete Markov model	Lifetime horizon Healthcare system perspective	Costs, QALY saved, and LY saved
Siebert et al. (2021) [32]	Patients aged <50 to >75 with dyspnea suspected of acute HF in ED (Trial Cohort)	USA	NT-proBNP-driven diagnosis vs. diagnostic strategy without NT-proBNP	Decision-tree model	6-months' time horizon US Medicare perspective	SAEs
Pufulete (2017): [37]	Patients with HF (HFrEF) in primary and secondary care (RCTs)	UK (primarily)	BNP-guided strategy compared with a standard clinically guided strategy	Markov model	Lifetime horizon UK NHS perspective	Costs and QALY
Jafari et al. (2018) [39]	Patients with HF (Systematic Review)	USA, UK, Canada, Switzerland	NT-proBNP-/BNP-guided care vs. usual/symptomatic/clinical care	Most studies used the Markov model,	Most studies used a lifetime horizon	Most studies used QALY
Mohiuddin et al. (2016) [33]	Recently hospitalized patients aged <75 to >75) with HFrEF or HFpEF. (hypothetical)	UK	Specialist-led BNP guided care vs specialist-led-clinically guided care	Markov model	Lifetime horizon	Costs and QALY
Morimoto et al. (2004) [34]	Patients (age 35-85) in outpatient care after hospitalization due to HF with LVEF <40% (hypothetical)	Japan	BNP measurement once every three months vs. no BNP measurement	Markov model	Nine months	Cost and QALY
Moertl et al. (2013) [38]	Patients with CHF intensive patient management. (RCT)	Austria, Canada	Usual care vs. multidisciplinary care vs. NT-proBNP guided intensive patient management	Markov model	20-year time horizon Payer perspective	Long-term costs and QALY
Heidenreich et al. (2004) [35]	Patients 60 years old men and women with LVEF < 40 % (hypothetical)	USA	BNP and echo (if abnormal) vs. BNP only vs. echo for all patients vs. no screening	Decision model	Lifetime horizon Societal perspective	Costs and QALY

4. Methods

4.1 Model Framework

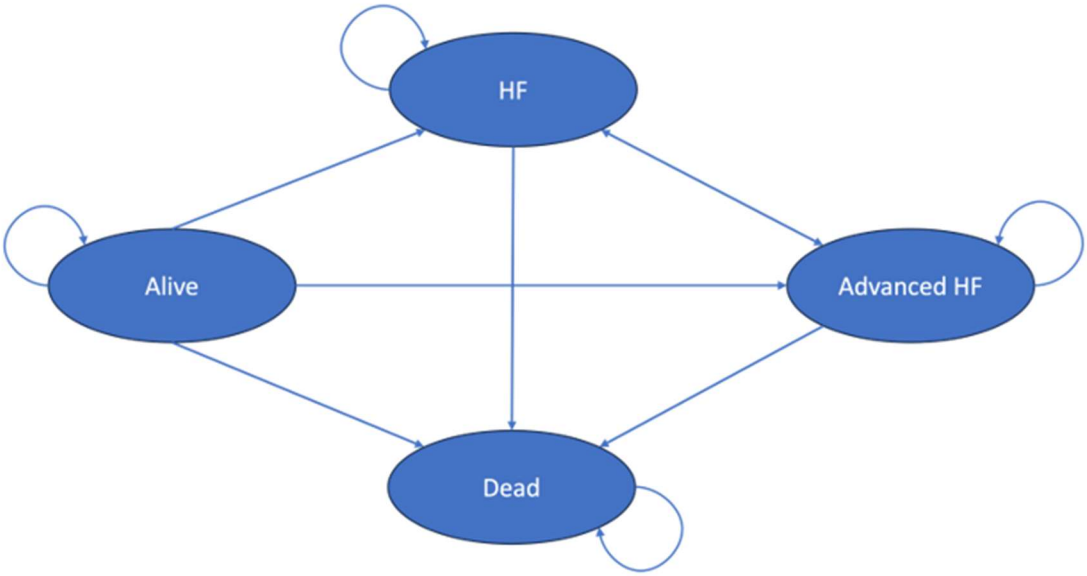

Figure 2: Markov Model

A decision analytical model approach is utilized to investigate the cost-effectiveness of annual screening with NT-proBNP cut-off at ≥ 400 pg/mL and SGLT2i treatment compared to current diagnostic practice (echocardiography) and Standard of Care (SoC) treatment of HF in T2DM patients in Danish ambulatory care. The model does not consider the categorization of HF. The cut-off value at ≥ 400 pg/mL is extracted from Taylor et al. (2023) [23].

A Markov model consisting of four health states has been developed using Microsoft Excel to cover the disease progression of T2DM and HF. The model has been developed based on the input gathered from the current research section of this analysis, the recommended patient flow from the DCS position paper, and the medical advisor input from AstraZeneca [8]. The model is illustrated in Figure 2.

The model inputs should originally be gathered from the Thousand&2 study. The study recruited 1030 patients with T2DM from the ambulatory care centers, SDC and CfD, from 2011 to 2013. The T2DM population in this Thousand&2 study was transferred from primary care to ambulatory care because of inadequate glucose levels or complications related to T2DM. The population underwent a "study visit," which entails their T2DM duration, current treatment, diet, BMI, and CVD status. The population also measured their biochemistry, and all had an echocardiography done [27]. The mean age for entering the model is based on the Thousand&2 cohorts and is 66 years [27].

However, the current analysis only considers certain characteristics within this cohort, such as age, chronic condition, and patient setting. The rest of the cohort is a hypothetical scenario, with 1000 T2DM ambulatory patients getting annual screening with NT-proBNP and SGLT2i treatment and 1000 T2DM ambulatory patients undergoing diagnostic practice and SoC treatment. The model will distinguish between the SoC arm and the NTproBNP+SGLT2i arm. The rest of the model input will be gathered from the literature. Unfortunately, the current analysis did not get enough data from the Thousadn&2 study, so it needed to incorporate data from the literature.

This Markov model's cycle length is one year, and the costs and effects are assessed over a five-year time horizon. The cycle length is one year due to the DCS guidelines, which recommend an annual inquiry about cardiovascular symptoms. The five-year time horizon was originally chosen based on the data that could be available from the Thousand&2 cohort, where a five-year age stratification would be the incorporated concept. The analysis would consider the stratifications proposed by the

However, the data wasn't available, so the current analysis utilizes a five-year time horizon, starting from the mean age of the hypothetical population. This cost-effectiveness analysis applies a limited societal perspective, excluding productivity loss. The current analysis will focus on cost, QALY, and HHF and include a discounted annual rate of 3.5 %. A willingness-to-pay (WTP) threshold of 260,000 DKK/QALY is applied to assess the cost-effectiveness.

4.1.1 Health States

The Markov model comprises four health states: 'Alive', 'HF', 'Advanced HF', and 'Dead'. The model framework is identical for the NT-proBNP+SGLT2i arm and the SoC arm. However, the arms differentiate in diagnostic methods and treatment, which will be outlined in the following.

The health state 'alive' includes T2DM patients in ambulatory care who are not known with HF. In the SoC arm of the model, 3,87 % of T2DM patients will 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 [8].

In the NT-proBNP+SGLT2i arm all patients in the health state 'Alive' will be screened with NT-proBNP. 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. All patients in 'HF' receive SoC treatment in the SoC arm, while patients in the

NT-proBNP+SGLT2i arm receive treatment with SGLT2i as a substitute for SoC.
From ‘HF’, patients can transition to ‘Advanced HF’, ‘Dead’, or stay in ‘HF’, which applies to 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 ten days during one cycle identical for both arms in the model.
From ‘Advanced HF’ patients can transition to ‘Dead’, ‘HF’, or they can be rehospitalized due to HF and hereby remain in ‘Advanced HF’. ‘Dead’ is an absorbing health state.
The ten-day hospitalization is based on the study by Ambrosy et al. (2014), which analyzed a handful of studies on the length of HHF. The current analysis considers all the studies included in Ambrosy et al. (2014) and takes the average length of HHF, which equals ten days of HHF [40].

4.2 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 [23], [35], [41], [42], [43], [44], [45]. 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 [46]. The costs are estimated based on studies, pharmaceutical prices, and DRG listings [10], [11], [47], [48], [49], [50]. Utility input is based on the studies reporting health state utility values (HSUV) for health states ‘Alive’, ‘HF’, and ‘Advanced HF’ [51], [52]. All model inputs are presented in Table 5.

Table 5: Model Input

Transition probabilities	**Probability**	**Source**
From 'alive' to 'alive'	0,954	Residual
From 'alive' to 'HF'	0,004	[35], [41]
From 'alive' to 'dead'	0,018	[43]
From 'alive' to 'advanced HF'	0,024	[42]
From 'HF' to 'HF'	0,483	Residual
From 'HF' to 'advanced HF'	0,353	[42]
From 'HF' to 'dead'	0,163	[44]
From 'advanced HF' to 'advanced HF'	0,250	[45]
From 'advanced HF' to 'HF'	0,400	Residual
From 'advanced HF' to 'dead'	0,350	[45]
Costs	**Cost (DKK)**	**Source**
Health state costs (annual)		
Alive	20.063,00	[10]
Heart failure	69.654	[10]
Advanced heart failure	128.157,00	[10], [11]
Diagnostic costs		
Echocardiography	2.026	[50]
NT-proBNP	264	[53]
Treatment costs (annual)		
SoC	4.432,75	[10]
SGLT2i	5.866,15	[47], [48], [49]
Utility	**Utility**	**Source**
Health state utilities		
Alive	0,752	[51]
HF	0,591	[51]
Advanced HF	0,587	[51], [52]
Age-related utility decrement		
Annual utility decrement T2DM + HF	-0,046	[54]
Annual utility decrement T2DM*	-0,011	[54]
Other input	**Input**	**Source**
The mean age for entering the model	65,5	[27]
Sensitivity and specificity		
NT-proBNP ≥ 400 pg/mL sensitivity	81,70%	[23]
NT-proBNP ≥ 400 pg/mL specificity	80,30%	[23]
Probability of developing HF with T2DM	3,87%	[41]
Probability of developing Symp. of HF	9,80%	[35]

4.2.1 Transition Probabilities

4.2.1.1 From 'Alive'

In the SoC arm, the transition probability from 'Alive' to 'HF' is based on the annual probability of developing HF when diagnosed with T2DM (3,87%) [41], and the annual probability of developing symptoms of HF when untreated for HF (9,8%) [35]. Thus, the transition probability from 'Alive' to 'HF in the SoC arm is 0,379 %.

In the NT-proBNP+SGLT2i arm, the probability of transitioning from 'Alive' to 'HF' is based on the probability of developing HF when diagnosed with T2DM (3,87%) [41] and the sensitivity of NT-proBNP with a cut-off value of ≥400 pg/mL (81,7%) [23]. Based on these parameters, the transition probability from 'Alive' to 'HF' when applied to the NT-proBNP+SGLT2i arm is 3%.

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 [42]. 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 [43].

The probabilities of transitioning from 'Alive' to 'Advanced HF' and 'Dead' are identical between treatment arms. The probability of staying in 'Alive' is the residual, equaling 95 % and 93 % for SoC and NT-proBNP+SGLT2i, respectively. All the abovementioned transition parameters and probabilities are listed in Table 5, and the transition tables for both the SoC arm and NT-proBNP+SGLT2i arm can be seen in Appendix B.

4.2.1.2 From 'HF'

In both treatment arms patients can transition from 'HF' to either 'Advanced HF', 'Dead', or stay in 'HF'. In the SoC arm, the probability of transitioning from 'HF' to 'Advanced HF' is based on the study by Cavender et al. (2015), which found that a 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 % [42].

The probability of transitioning from 'HF' to 'Dead' is based on a study by Johansson et al. (2014), which found a 5-year rate of all-cause mortality among patients with T2DM and HF [44]. This corresponds to a 1-year probability of 16,3%.

In the NT-proBNP arm, these probabilities will be affected by the efficacy of SGLT2i identified in a meta-analysis. The probability of staying in 'HF' is the residual equaling 48,3 % for the SoC arm

and 62,1 % for the NT-proBNP+SGLT2i arm. All the above-mentioned transition probabilities are listed in Table 5, while the efficacy of SGLT2i will be presented in Section 6.1. The transition tables for both the SoC arm and NT-proBNP+SGLT2i can be seen in Appendix B.

4.2.1.3 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)[45]. The study reported that 25 % of patients with HHF were re-hospitalized within one year, and 35 % died from any cause within one year [45]. 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 equaling 40 %. The transition tables for both the SoC arm and NT-proBNP+SGLT2i can be seen in Appendix B.

4.2.2 Costs

4.2.2.1 Health State Costs

All the costs included in this analysis are converted to Danish Krone (DKK) since the current analysis considers a Danish setting. The health state costs are extracted from the study by Sortsø et al. (2016), examining the societal costs of DM in Denmark, and the study by Bundgaard et al. (2019), examining the Danish economic burden of HF [10], [11]. The study by Sortsø et al. (2016), which included direct and indirect costs, found that the total cost per person-year for DM patients without complications associated with secondary care was 20.063 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 69.654 DKK [10]. The costs associated with no complications and major complications are applied to the health states 'Alive' and 'HF', respectively.
The study by Bundgaard et al. (2019) found that the average annual direct cost related to HHF was around 58.504 DKK with a length of hospital stay between 4 and 20 days [11]. The cost of 'Advanced HF' is based on the cost associated with HHF from Bundgaard et al. (2019) and the total cost per person-year for DM patients with major complications from Sortsø et al. (2016), which equals an annual cost of 128.158 DKK [10], [11]. Appendix C creates a detailed schematic view of the annual health state costs.

4.2.2.2 Diagnostic Costs

Since the hypothetical patient setting is Danish, it was possible to gather diagnostic costs from Danish sources. The diagnostic costs for echocardiography are extracted from the diagnosis-related groups (DRG) listings for 2024. However, the listing does not specifically categorize echocardiography into a DRG listing. So, the current analysis assumed that the DRG 05PR04 code

for extended cardiology examination is categorized as echocardiography for 2024 for 2.026 DKK [50]. The diagnostic costs for NT-proBNP are based on prices from the clinical and biochemical departments at Frederiksberg and Bispebjerg Hospital. The cost of one NT-proBNP analysis is set at 264 DKK [53]. The NT-proBNP arm is charged for NT-proBNP analysis since the whole population is screened with this plasma marker.

5.2.2.3 Treatment Costs

The costs regarding treatment are based on an annual basis. For SoC treatment, the costs are extracted from the study by Sortsø et al. (2016). The current analysis considers pharmaceutical drug costs from Sortsø et al. (2016) with DM patients who have no complications minus the cost of DM with major complications to create an annual cost of SoC treatment for HF. This amounts to 4.432,75 DKK [10].

The other treatment cost is the annual cost of incorporating SGLT2i while getting screened with NT-proBNP. In Denmark, there are different types of SGLT2i, depending on the pharmaceutical company and the indication associated with each medication. The current analysis considers all the available SGLT2i in the Danish market. The pricing data is extracted from the Danish Medicines Agency and considers three different types of SGLT2i: Dapagliflozin, Empagliflozin, and Canagliflozin. To create an estimated price for the SGLT2i, the analysis calculates the price per year for each medication and an average for all of them. This amounts to 5.866,15 DKK annually for SGLT2i treatment [47], [48], [49]. Appendix D will visualize more details regarding the treatment and diagnostic costs.

4.2.3 Utility

The current analysis uses Health-related Quality of Life (HRQoL) measures to calculate health-state utility values (HSUV) when the T2DM ambulatory population has comorbidities. HRQoL data is extracted from Hvidberg et al. (2023), which utilized the EQ-5D-3L instrument to calculate HRQoL among a Danish population to define chronic conditions based on ICD-10 codes. The extracted HSUV for the health state ‘Alive’ is at 0,752, while the health state ‘HF’ is at 0,678 [51].

To calculate the HSUV comorbidities, this analysis uses the multiplicative methods from Ara et al. (2017) [55]. The needed values to utilize the multiplicative method are having a population with no history of T2DM, no history of HF, and no history of both. The extracted value for the population that has no history of both T2DM and HF is assumed to be from HSUV, SF-12 general health at an excellent level at a value of 0,974 since the population has no health-related problems. The no history of T2DM and no history of HF are “having no chronic conditions” – HSUV since both

disease areas are chronic conditions [51]. Utilizing the multiplicative method to estimate the HSUV for comorbidities, the estimated HSUV for the health state ‘HF’ is calculated to be 0,591.
This analysis uses Gu et al. (2020) to calculate the HSUV for the ‘Advanced HF’ health state. The study focuses on the HRQoL for T2DM patients when hospitalized due to complications, and it reports a mean HSUV for hospitalized HF patients of 0,47 and 0,591 [52].
When considering a hospitalization duration of 10 days and a Markov Model cycle length of one year, the adjusted HSUV for ‘Advanced HF’ is calculated to be 0,5837 [52].
The analysis uses a five-year time horizon with a cycle length of one year, which means that the analysis needs an age-related utility, which is gathered from Keng et al. (2022) [54]. Keng et al. (2022) analyze the use of utility decrements in a diabetic population, where they estimate an annual utility decrement of -0,046 for T2DM and -0,011 for HF [54]. The utility decrements are added to each cycle year within the Markov trace. Appendix E shows a detailed schematic view of the utility inputs and the formulas utilized.

4.3 Meta-analysis

In the current analysis, the meta-analysis analyzes the hazard ratios for treating SGLT2i within HHF and all-cause mortality for T2DM being screened with NT-proBNP. The reason for choosing hazard ratios as a measurement for the efficacy of SGLT2i treatment when getting screened with NT-proBNP is the interpretation of hazard ratios as a risk reduction [56].

The reason for the incorporation of SGLT2i treatment while being screened is because SGLT2i is the primary medication for T2DM patients with HF, which the DCS states [9].

A literature search needed to be conducted in order to create a meta-analysis, which starts with a PICO model to establish the search terms and to conduct a search string. The comparator part of the PICO model is excluded to create a broader search in order to identify relevant articles. The PICO model can be seen in Table 6, while the search string is available in Appendix F. The established search string depends on the search terms that can be seen in the PICO model, Table 6. The studies identified from the PubMed database were then screened through a PRISMA flowchart [30], which can be seen in Figure 3.

Table 6: PICO model with no comparator

P	I	C	O
Heart failure patients Systolic heart failure Diastolic heart failure Diabetes Mellitus Type 2	Sodium-Glucose Transporter 2 Inhibitors Sodium-glucose Transporter 2		Hospitalization Mortality

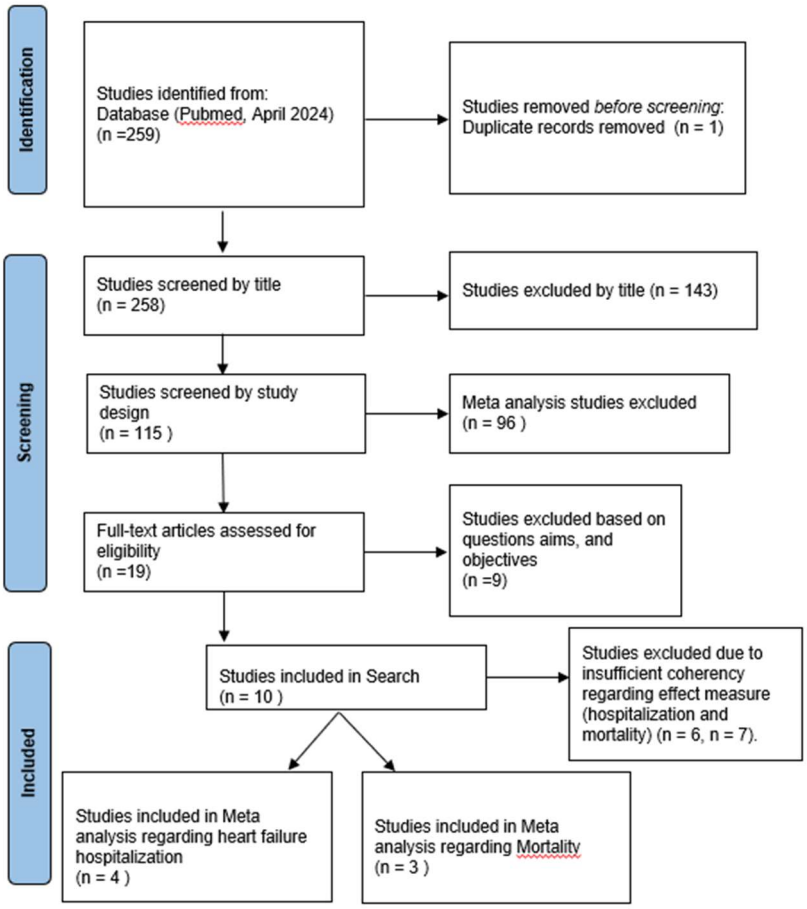

Figure 3: PRISMA-flowchart visualizing the identification, screening, and number of included studies in both meta-analyses.

The literature search for the meta-analysis resulted in 258 hits (259, including duplicates, which were removed before screening). The studies were screened by title, then study design, and 96 were excluded due to being meta-analyses. This resulted in 19 hits, which were full text assessed and resulted in nine studies that got excluded due to not being relevant regarding their study objective. Ten studies were left, of which six were excluded due to insufficient coherency regarding effect measures for HHF and seven studies regarding all-cause mortality. The literature search resulted in four studies that can be included in the meta-analysis regarding HHF and three studies regarding all-cause mortality. The studies included for HHF are as follows: Kato et al. (2019), Cosentino et al. (2020), Fitchett et al. (2019), and Rådholm et al. (2018) [57], [58], [59], [60]. The studies included for all-cause mortality are as follows: Kato et al. (2019), Fitchett et al. (2019), and Rådholm et al. (2018) [57], [59], [60]. The trials implemented, with their individual source, are as follows: Wiviott et al. (2019) (DECLARE-TIMI 58), Consentino et al. (2020) (VERTIS CV), Steiner et al. (2016)

(EMPA-REG OUTCOME), and Neal et al. (2017) (CANVAS program) [58], [61], [62], [63]. Table 7 shows the studies and their associated trials utilized for the meta-analysis.

Table 7: Studies from the literature search and their associated trials

Study	Associated trial
Kato et al. (2019)	DECLARE-TIMI 58
Cosentino et al. (2020)	VERTIS CV
Fitchett et al. (2019)	EMPA-REG OUTCOME
Rådholm et al. (2018)	CANVAS program

The studies regarding both outcomes do not include the needed hazard ratios for HHF and all-cause mortality values. Therefore, the current analysis focuses on trials with coherent results that can be compared in a meta-analysis. It's important to note that the studies included in the meta-analysis literature search all have trials associated with each of them. The trials also do not distinguish between the different types of heart failure, which creates the assumption of all the different types of HF as one category.

The included trials in the meta-analysis all focus on different types of SGLT2i, compared to the placebo group, while the placebo group still includes standard-of-care diabetes therapy. The trials measured HHF and all-cause mortality using the hazard ratio with a 95% confidence interval (CI). However, in one trial, VERTIS CV [58], did not measure all-cause mortality, which excludes the trial from that part of the meta-analysis.

The data calculation for the meta-analysis will be conducted using the STATA software to create a pooled estimate, I-squared, and P-value. Using Excel, the data will be visualized as a forest plot, showing each HR for all trials, HHF and all-cause mortality. The meta-analysis will consider utilizing a fixed-effect model due to the limited number of trials included in the current analysis, as well as the probability of less heterogeneity between the trials[64].

4.4 Sensitivity Analysis

A one-way DSA is conducted on the NT-proBNP + SGLT2i arm versus the SoC arm regarding ICER as DKK/QALY to look at the uncertainties regarding the multiple parameters within the Markov model. The parameters of interest include an upper and lower bound, defined as a confidence interval (CI) only if available. For the parameters that aren't provided with a CI by the literature, the upper and lower bounds parameter value was adjusted by 20 % or 50 % for both ends. The costs for health state 'alive', 'HF', 'Advanced HF', and the SoC treatment and SGLT2i treatment are adjusted with a 20 % at upper and lower bounds. The cost of echocardiography and NT-proBNP are adjusted at a value of 50 % due to the study by Mohiuddin et al. (2016), which tested the sensitivity of the intervention by 50 % [33].

The parameters of HR all-cause mortality and HR HHF CIs are gathered from the fixed-effect model meta-analysis pooled estimates. The upper and lower bound parameter for both NT-proBNP specificity and sensitivity is extracted from Taylor et al. (2023) [23]. The probability of developing HF was applied with a 20 % at the upper and lower bound, while the probability for developing symptoms is extracted from Heidenreich et al. (2004) [35], with an upper and lower bound at 15 % and 5 %, respectively.

4.5 Scenario Analysis:

The current analysis will also conduct a scenario analysis around the base case results based on an NT-proBNP cut-off at ≥ 400 pg/mL from Taylor et al. (2023). The NT-proBNP cut-off and its respective sensitivity and specificity are extracted from Taylor et al. (2023). It would be an ideal setup to produce a scenario analysis based on different cut-off values for NT-proBNP, which are also extracted from Taylor et al. (2023) [23]. The cut-offs included in this scenario analysis will be ≥ 125 pg/mL and ≥ 2000 pg/mL, and the sensitivity and specificity are 94,6 % and 50 %, respectively, for ≥ 125 pg/mL, while 38,9 % and 96,1 %, respectively, for ≥ 2000 pg/mL [23]. The cut-off values do somewhat coincide with the DCS-position paper; however, they don't showcase any sensitivity or specificity for NT-proBNP [8]When conducting the scenario analysis, it will be presented as results such as the total cost QALY and total cost per HHF. Table 8 illustrates the scenario analysis's sensitivities and specificities.

Table 8: Sensitivity and specificity for scenario analysis [23]

NT-proBNP	≥ 125 pg/mL	≥ 400 pg/mL	≥ 2000 pg/mL	Source
Sensitivity	94,60%	81,70%	38,90%	Taylor et al.
Specificity	50%	80,30%	96,10%	(2023)

5. Results

5.1 Meta-analysis

This section presents an overview of the trials included in the meta-analysis. Table 9 shows the trials utilized within the meta-analysis and briefly describes the included population and number of participants. The intervention differs from every trial, while the Standard-of-care diabetes therapy for all the trials is a placebo. Table 9 also shows the mean HR for HHF and all-cause mortality with a 95 % CI.

Table 9: Trials utilized within the meta-analysis.

Trial	**Population**	**Intervention vs Comparator**	**HHF HR**	**All-cause mortality HR**
(Source)	(n)	(dose)	mean (95 % CI)	(95 % CI)
DECLARE-TIMI 58 (Wiviott et al. 2019) [61]	>40 years old T2DM patients, multiple risk factors, or established ASCVD (17.160)	Dapagliflozin (10 mg) vs Placebo	0,73 (0,61 – 0,88)	0,73 (0,61 – 0,88)
VERTIS CV (Cosentino et al. 2020) [58]	> 40 years old T2DM patients with established ASCVD (8.246)	Ertugliflozin (5 mg or 15 mg) vs Placebo	0,70 (0,54 – 0,90)	NR
EMPA-REG OUTCOME (Steiner et al. 2016) [62]	> 18 years old T2DM, established CVD (7.020)	Empagliflozin (10mg or 25 mg) vs Placebo	0,65 (0,50 – 0,85)	0,68 (0,57 – 0,82)
CANVAS Program (Neal et al. 2017) [63]	>30 years old T2DM with symptomatic ASCVD or >50 years old T2DM with 2 or more CVD risk factors (10.142)	Canagliflozin (300 mg or 100 mg) vs Placebo	0,67 (0,52 – 0,87)	0,87 (0,74 – 1,01)

5.1.1 Forest Plot

Using a fixed-effect model, the meta-analysis is visualized through a forest plot between the four trials for HHF and three trials for all-cause mortality. Both Forest plots compare the usage of SGLT2i and placebo in populations with T2DM patients, with an HR and weighted average between the trials. When considering the HHF forest plot, all the trials favor the SGLT2i treatment compared to the placebo.

The pooled estimates between all four trials show that the SGLT2i is favorable compared to placebo, with a 95 % confidence interval that doesn't cross the line of no effect. The I-squared shows 0 % heterogeneity between the trials, with a p-value of 0,898, indicating insignificance within the comparison of the four trials when utilizing SGLT2i versus placebo. The risk reduction of being HHF when using the treatment of SGLT2i will be 31 %. The HHF forest plot can be seen in Figure 4.

When considering the all-cause mortality forest plot, all three trials' hazard ratios favor the SGLT2i treatment compared to the placebo. The 95 % confidence interval crosses the line of no effect for the trial DECLARE-TIMI 58 and CANVAS program. The pooled estimate between all three trials shows that SGLT2i is favorable compared to placebo, with a confidence interval (95 %) that doesn't cross the line of no-effect. The I-squared shows 78 % heterogeneity between the trials, with a p-value of 0,011, indicating significance between the trials. The risk reduction of all-cause mortality when using the treatment of SGLT2i will be 17 %. The all-cause mortality forest plot can be seen in Figure 5. The pooled estimates are utilized in the transition probabilities from 'HF' to 'Advanced HF' for the hazard ratio for HHF and from 'HF' to 'Dead' for the hazard ratio for all-cause mortality.

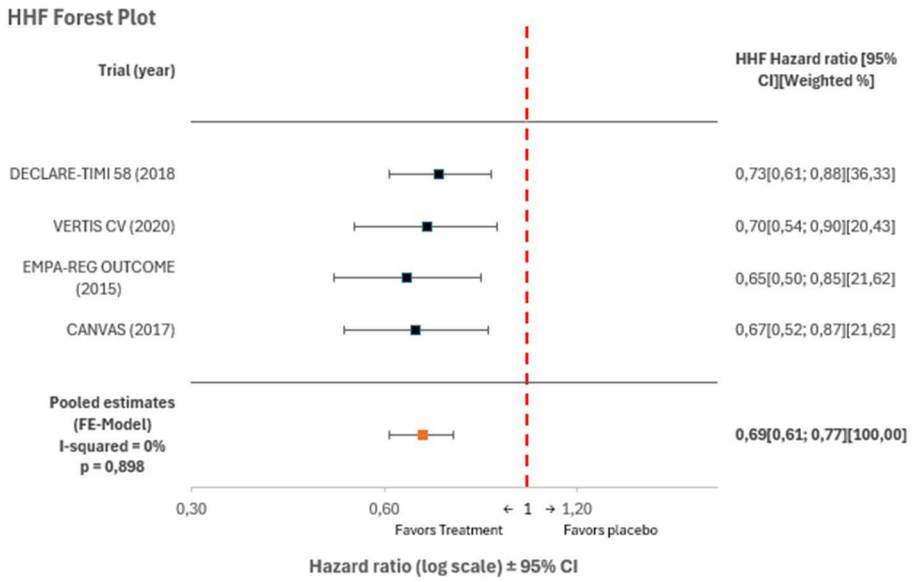

Figure 4: Forest plot showcasing Hazard ratios, plotted on a logarithmic scale, for Heart failure hospitalizations between four trials when utilizing SGLT2i versus placebo. The forest plot considers a fixed-effect model approach, with I-squared and p-value.

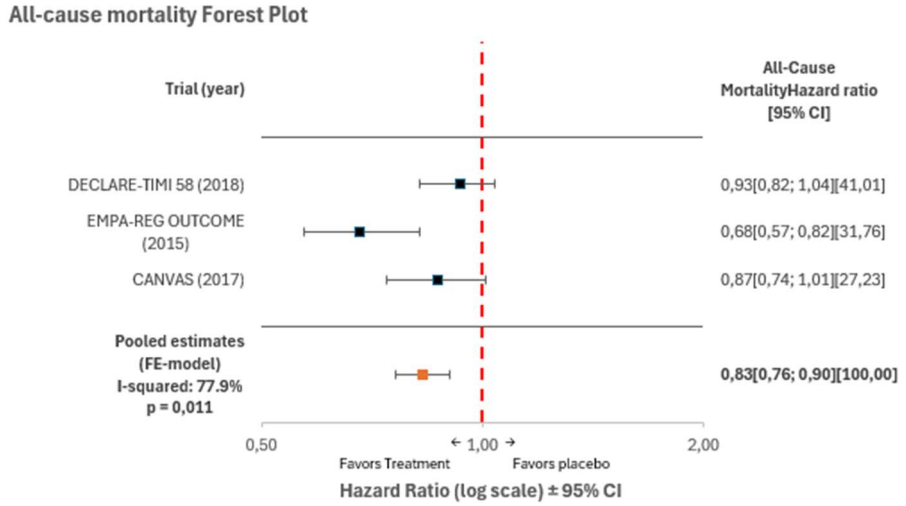

Figure 5: Forest plot showcasing Hazard ratios, plotted on a logarithmic scale, for All-cause mortality between three trials when utilizing SGLT2i versus placebo. The forest plot considers a fixed-effect model approach, with I-squared and p-value.

5.2 Base-case Cost-effectiveness Analysis

Table 10 presents the base-case cost-effectiveness analysis results from the Markov model. The base-case results show the discounted cost-effectiveness between the NT-proBNP+SGLT2i arm and the SoC arm when utilizing an NT-proBNP cut-off of 400 pg/mL.

The base-case model results per patient show that utilizing the NT-proBNP+SGLT2i arm, compared with the SoC arm, has an incremental cost of 1.503 DKK, meaning that the NT-proBNP+SGLT2i arm is the more expensive option. However, considering the HHF, the incremental difference between the two is -0,36, which means there are fewer HHF when comparing the NT-proBNP+SGLT2i arm compared to the SoC arm. There is also an incremental QALY gain of 0,0237 between the two arms.

Table 10: Base case model results per patient

	NT-proBNP+SGLT2i	SoC	Incremental
Total costs (DKK)	98.039,93	96.537,33	1.502,61
HHF	0,46	0,81	-0,36
QALYs	2,2788	2,2551	0,0237

The ICERs are presented in Table 11. The ICERs are presented as the total cost per HHF at - 4.174 DKK/QALY and the total cost per QALY gained at 63.400 DKK/QALY. Utilizing a 260.000 DKK/QALY WTP threshold, the NT-proBNP+SGLT2i arm is more costly than the SoC arm. However, the effect is better considering QALY.

Table 11: Base case cost-effectiveness results

ICERs		
Total cost per HHF	-4.174	DKK/QALY
Total cost per QALY	63.460	DKK/QALY

The cost-effectiveness place illustrates that the ICER for a total cost per QALY, at 63.400 DKK/QALY, is placed in the northeast quadrant, below the cost-effectiveness threshold (Figure 6).

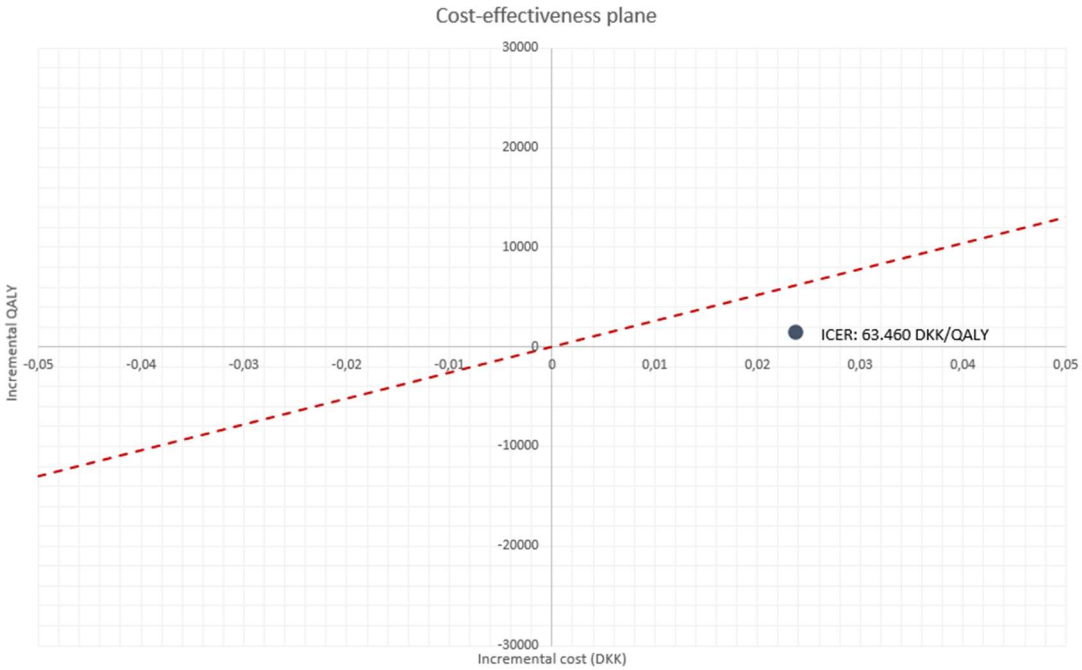

Figure 6: Base case cost-effectiveness plane.

5.3 Sensitivity analysis

5.3.1 One-way Sensitivity Analysis

The one-way DSA is visualized as a tornado plot with specific parameters of interest. Figure 7 shows the one-way DSA for the NT-proBNP+SGLT2i arm compared to the SoC arm, based on the 63.400 DKK/QALY ICER, and incorporates parameters with their respective lower and upper bounds.

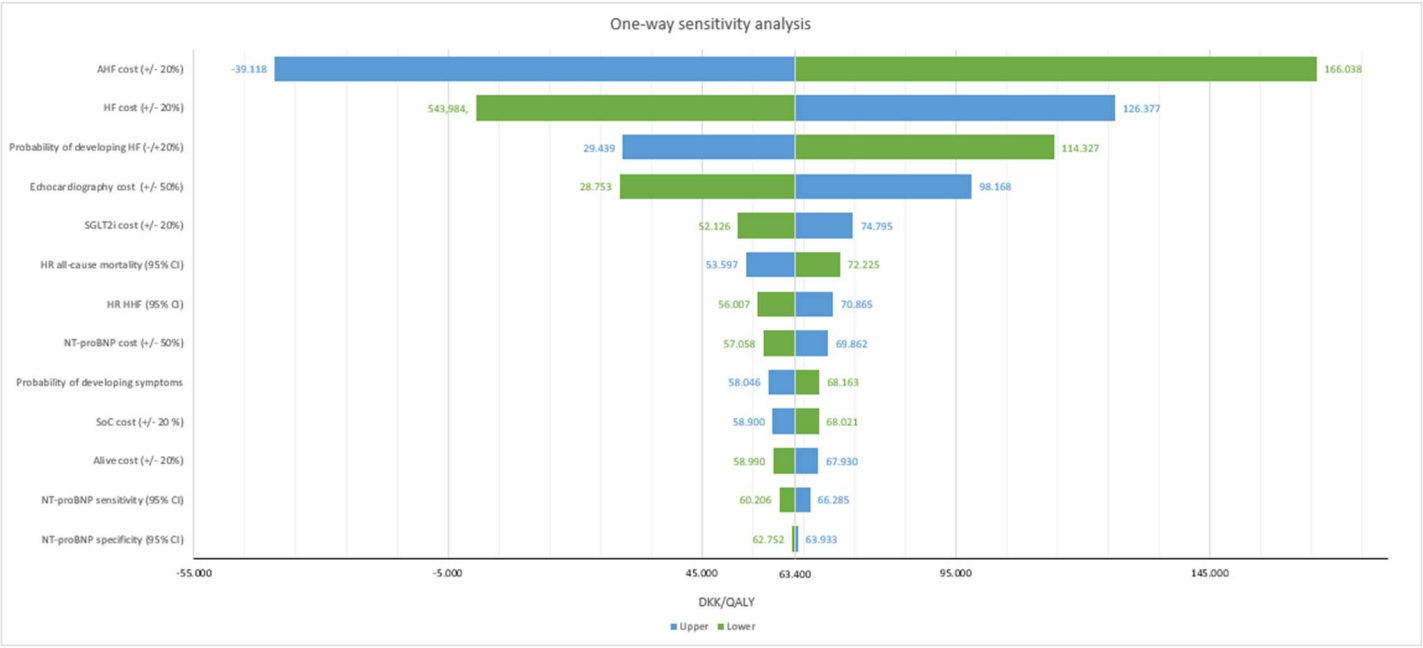

Figure 7: Tornado plot depicting the one-way sensitivity analysis.

The parameters most sensitive to the model are the costs related to the health 'Advanced HF' and the health state 'HF'. The model is the least sensitive to the uncertainty of the sensitivity and specificity of NT-proBNP at a cut-off of ≥ 400 pg/mL.

5.3.2 Scenario Analysis

The scenario analysis for the NT-proBNP cut-off ≥ 125 pg/mL shows that incremental cost is higher at 3.527 DKK, with HHF and QALYs being slightly different from the base-case results. The scenario analysis for the NT-proBNP cut-off at ≥ 2000 pg/mL shows an incremental cost of -5.013, illustrating that the NT-proBNP+SGLT2i arm is less expensive than the SoC arm. There is a slight increase in HHF compared to the base-case results and for NT-proBNP cut-off ≥ 125 pg/mL. However, there is an increase in the incremental QALY of 0,034.

When considering the ICERs for the scenario NT-proBNP cut-off ≥ 125 pg/mL, all the ICERs have increased compared to the base-case results. The ICER for a total cost per QALY, 171.026 DKK/QALY, shows NT-proBNP+SGLT2i is still cost-effective when considering a WTP threshold of 260.000 DKK/QALY.

When looking at the scenario of NT-proBNP cut-off at ≥ 2000 pg/mL, it is very prominent that at an ICER off -147.507 DKK/QALY, the NT-proBNP+SGLT2i is less expensive and has a better effect compared to SoC.

Table 12: Scenario Analysis (NT-proBNP cut-off ≥125 pg/mL and >2000 pg/mL)

Scenario 1: NT-proBNP cut-off ≥ 125 pg/mL			
	NT-proBNP+SGLT2i	**SoC**	**Incremental**
Total costs (DKK)	100.065	96.537	3.527
HHF	0,45	0,81	-0,37
QALYs	2,2758	2,2551	0,0206
ICERs			
Total cost per HHF	9.533 DKK/QALY		
Total cost per QALY	171.026 DKK/QALY		

Scenario 2: NT-proBNP cut-off ≥ 2000 pg/mL			
	NT-proBNP+SGLT2i	**SoC**	**Incremental**
Total costs (DKK)	91.524	96.537	-5.013,00
HHF	0,49	0,81	-0,33
QALYs	2,2891	2,2551	0,034
ICERs			
Total cost per HHF	-15.191 DKK/QALY		
Total cost per QALY	-147.507 DKK/QALY		

The incremental cost-effectiveness plane illustrates that the ICER for the≥ 125 pg/mL scenario is placed in the northeast quadrant. This makes it more expensive and slightly decreases the incremental QALY; however, the ICER is still below the WTP threshold. The ICE-plane also illustrates the scenario of ≥ 2000 pg/mL, which is at the southeast quadrant, making it less expensive and more effective, creating a scenario where NT-proBNP+SGLT2i is more dominant compared to the base-case results (ICE-plane can be seen in Figure 8).

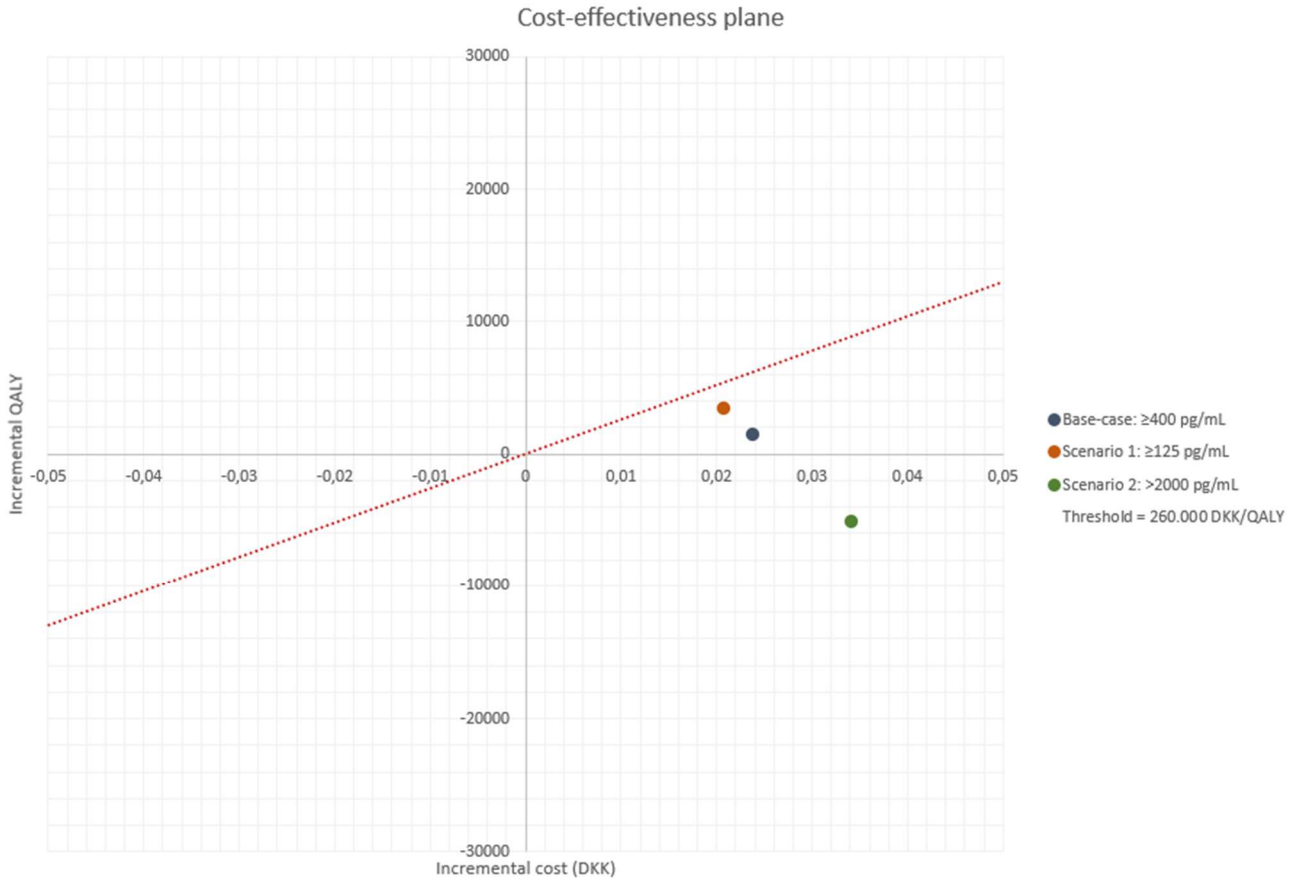

Figure 8: Cost-effectiveness plane: Scenario analysis.

6. Discussion

6.1 Principal findings

The base-case results show an incremental cost of 1.503 DKK between the NT-proBNP and SoC arms. Considering the WTP threshold, both arms are cost-effective.
However, there is a reduction in HHF at - 0.36 per patient, which suggests a lower number of T2DM ambulatory patients getting HHF. Also, an incremental QALY gain of 0,0237 is showcased. The ICERs calculated from the current analysis are -4.174 DKK per HHF and 63.400 DKK per QALY. These base-case results are calculated based on an NT-proBNP cut-off of 400 pg/mL and are evaluated against a WTP threshold of 260.000 DKK/QALY. This indicates that the NT-proBNP+SGLT2i arm is cost-effective.
The HHF at - 4.174 DKK indicates that even though the NT-proBNP + SGLT2i arm is more expensive, by decreasing the HHF, there is a possibility to save on cost.
The base-case results correlate to some of the studies in the current research section. Both Walkey et al. (2023) [36] and Siebert et al. (2021) [32] showed NT-proBNP to be cost-effective. Siebert et al. (2021) support routine measurements of NT-proBNP to help guide HF diagnosis, which is incorporated into the current analysis model [32]. It's also worth noting that the cost of NT-proBNP is added to the whole hypothetical population, creating a substantial utilization of resources. Still, it does decrease the rate of getting HHF.
The one-way DSA shows that the cost of health state, 'Advanced HF', and the cost 'HF' are the parameters most sensitive to the model, while the parameters of NT-proBNP sensitivity and specificity are the least sensitive to the model.
This does state that the cost for health state 'Advanced HF' is the main driver for this model, which is associated with the high cost associated with being hospitalized with HF. This correlates with the knowledge presented in the background section, provided by Bundsgaard et al. (2019), highlighting the economic burden of HHF [11].
The current analysis also conducted a scenario analysis. At a cut-off of ≥ 125 pg/mL, there is an incremental cost of 3.527 DKK, with slight differences in HHF and QALYs. The ≥ 125 pg/mL ICER was more expensive than the base-case results but was cost-effective at 171.026 DKK/QALY. For the cut-off of ≥ 2000 pg/mL, the incremental cost of -5.013 DKK, which makes the NT-proBNP+SGLT2i arm less expensive, although a decrease in HHF, and the incremental QALY has

increased to 0,0304. The cut-off for the ≥ 2000 pg/mL scenario ICER is at -147.507 DKK/QALY, making it dominant since the cost is lower and has a better effect than SoC.

6.2 Meta-analysis

The current analysis' meta-analyses are based on the DCS guidelines, which states that SGLT2i is the most effective treatment for T2DM patients with HF [9]. None of the current studies focus on SGLT2i as a treatment aspect within their population. However, since SGLT2i treatment is only given to T2DM patients with HF, only one study included this in their population (Walter et al. (2023) [31]) but does not measure the effect that SGLT2i might have on the population.

The trials involved in the studies were different SLGT2i's, where each was compared against a placebo group, which received standard-of-care diabetes therapy. However, it's important to note that the standard-of-care diabetes therapy was not explained in detail in the trials included. This limits the interpretation of results since a more precise treatment explanation would create a more realistic patient setting and change into more precise cost measures.

The meta-analysis was showcased through two forest plots for HHF and all-cause mortality. In the forest plot HHF, there was no heterogeneity within the pooled estimate, which could support the risk reduction of HHF since the results can be interpreted as homogenous.

The other forest plot, for all-cause mortality, showcased two trials CIs crossing the line of no effect, which can be interpreted as there is no difference within the trials. However, the pooled estimate did show a risk reduction in all-cause mortality. The forest plot I-squared does show heterogeneity between the trials, and with a significant p-value. However it's important to note that the number of trials included is limited.

The HHF and all-cause mortality measures are interesting effect measures to incorporate into the model. However, there are multiple aspects regarding the SGLT2i. All the trials included within the meta-analysis illustrate endpoints such as adverse events, Major adverse cardiac events (MACE), CVD death, and renal outcomes. These are highly measured endpoints within all the trials and might be interesting to incorporate in further analysis [58], [61], [62], [63].

The model used for the meta-analysis was a fixed-effect model. The model's construction followed the paper by Tufaranu et al. (2015), which discusses the models needed to be implemented within a meta-analysis [64]. Tufaranu et al. (2015) recommend that meta-analysis models with less than five trials align with the recommendation for their usage. However, it's important to note that the fixed-effect model relies on the assumption of homogeneity between the outcome measures and trials

[64]. This may not be an appropriate use of a fixed-effect model when considering that the all-cause mortality results did show heterogeneity between the trials. However, the lower heterogeneity between the trials for HHF does support the use of a fixed-effect model. The all-cause mortality meta-analysis results may benefit from utilizing a random-effect model to generalize the results since the pooled estimates show heterogeneity. However, Tufaranu et al. (2015) recommend including more trials to create a sufficient model [64]. The current analysis could further investigate incorporating more trials within the meta-analysis to create a more nuanced approach regarding the SGLT2i treatment.

6.3 Model framework

The Markov model creates a CEA utilizing the plasma marker NT-proBNP as an annual screening tool, with the addition of SGLT2i treatment for HF in T2DM patients within a Danish ambulatory care setting. This is compared to the current diagnostic practice, which uses echocardiography and SoC treatment.

What might be one of the strengths of this analysis is the utilization of a cut-off at ≥ 400 pg/mL for NT-proBNP. As mentioned, the value is extracted from Taylor et al. (2023), and the current analysis model utilizes this value as the base case [23]. When comparing this to the DCS position paper [8], which recommends a cut-off of ≤ 125 pg/mL to rule out HF, it can be argued that the current analyses identify T2DM patients who are at a higher risk since the assumption of ≥ 400 pg/mL excludes the patients under that level. However, it is worth highlighting that both the DCS-position paper and Taylor et al. (2023) focus on a primary care setting. In contrast, the current population is ambulatory T2DM patients treated in specialized clinics.

However, the DCS position paper states that ≥ 450 pg/mL is categorized as high-risk patients aged <50 years [8]. This could be a sufficient interpretation of overall high-risk patients being analyzed in this current analysis.

The Markov model also uses a five-year time horizon. This is based on the data that were anticipated to be available from the Thousdan&2 study. The clinicians working with the database argued for five-year stratification, starting from the youngest or choosing the average age as the starting point and comparing the stratifications together. Since the data wasn’t available, the analysis only focuses on a five-year horizon, starting from the mean age of the Thousand&2 study.

When dealing with a Markov model, an extended time horizon might be a sufficient method to incorporate to capture the long-term costs and effects associated with the population [65]. Comparing this to the current research section in this analysis, it's prominent that a lifetime horizon may be the most efficient analysis method. Drummond et al. (2015) also state that the choice of this model type is correct since the current analysis focuses on two chronic conditions and that a lifetime time horizon might be the most accurate way of dealing with this scenario [65].

One of the actions chosen in this current analysis is choosing a WTF threshold of 260.000 DKK/QALY gained based on the NICE guidelines [66]. The threshold chosen is the maximum amount to pay for one additional QALY gained. However, when comparing the high WTP threshold, it's prominent that the results are all cost-effective, even when lowering the threshold. Conversely, the WTP threshold is a British guideline and does not correlate with the Danish healthcare system, and the WTP threshold is usually based on CUA and not CEA [65], [66]. The analysis could implement the NICE guidelines threshold spanning from 20,000 to 30,000 pounds to visualize the cost-effectiveness of the two arms.

One of the decisions was also the choice of a limited societal perspective. By doing this, the analysis excludes productivity loss and may underestimate the national impact on costs that T2DM and HF have. The reason for choosing a limited societal perspective is due to the recommendation by the Danish Medicines Council, which states that the effect measure should be presented as QALY and needs to include all relevant costs associated with the treatment [67].

As stated, HF is a costly chronic disease, but it's not only the direct costs that have an impact; also, the indirect cost has a major impact on the Danish welfare system. It has been demonstrated that HF leads to productivity loss, and around 25 % of patients dealing with HF do not resume their work after one year of their first HHF [6]. So, by including the productivity losses, the analysis might create a more realistic cost setting.

It is also important to highlight the challenges and limitations of the model framework. The current analysis is hindered by data limitation due to the incomplete data from the Thousand&2 study. Therefore, the current analysis had to gather data from the literature, creating a problem regarding internal validity. All the model inputs are gathered from different sources, which are not exclusively extracted from the current research section. This creates a lot of uncertainties since it would be more viable to have concrete data from the Thousand&2 study to create a model and population that's representative of the Thousand&2 study. Also, the current analysis utilizes a hypothetical population of 1000 T2DM patients, where some of the base case characteristics are extracted from

the Thousand&2 study, which hinders the full potential of the actual population.
The model also prioritized not categorizing HF within the different kinds of HF and incorporates all kinds. The Thousand&2 study does have the ability to categorize HF within the population [25]. This creates a less nuanced analysis with the treatment of the HF and the disease progression. The model accuracy is affected by choosing not to categorize HF and may influence costs and effect measures. This reduces the precision of the overall analysis when dealing with such a complex chronic disease.

6.3.1 Transitions probabilities

The NT-proBNP + SGLT2i arm is designed for annual screening in T2DM patients with HF. When including the sensitivity of NT-proBNP (81,7%), the probability of going from the health state 'Alive' to 'HF' is much higher than that of the SoC arm, which creates a scenario where 3 % of the hypothetical population transitions to the 'HF' health state from 'Alive'. However, fewer T2DM are getting HHF due to the SGLT2i treatment, which causes a risk reduction. By adding the SGLT2i for all-cause mortality, there is also a slight decline in the number of patients dying, which can be seen in Appendix B's transition tables.
However, it's important to note that both arms' transition probabilities are extracted from various studies selected to fit the Markov model. The studies don't necessarily incorporate all the aspects of the population, like the one with this current analysis. The studies utilized for the transition probabilities vary in the populations, healthcare system, and patient settings. These limiting factors must be highlighted since they don't represent the population in a Danish context. Also, many transition probabilities are identical between the two arms; while this may provide some foundation, it does not fully create a nuanced patient flow. However, the Markov model is the same for both hypothetical populations, which does create an easier interpretation of the patient flow when only changing certain parameters to look at the difference between the two arms.

6.3.2 Cost input:

The health state costs are extracted from Danish studies to contextualize the local population and health care. The sources used are Sortsø et al. (2016), which looks at the overall societal costs of DM in Denmark [10], and Bundgaard et al. (2016), which looks at the economic burden of HF in Denmark [11]. There are significant limitations when using Sortsø et al. (2016) [10] as the definitive source of health state costs. Sortsø et al. (2016) [10] only look at the overall societal cost

of DM and do not include a category for T2DM only. The study also creates broad categorizations within the stratification of complications. Major complications do highlight that HF is part of that but does not specify if there are any other complications associated with them. This could be hospitalization or if there are some treatments incorporated in the major complications category. This could result in double counting if the category includes hospitalization and overestimates costs since Sortsø et al. (2016) also include direct and indirect costs in their calculations.
The treatment costs are also associated with some limitations. The SGLT2i treatment cost is the average annual price when combining Dapagliflozin, Empagliflozin, and Canagliflozin. Incorporating one specific medication would be more precise to create a more accurate analysis. However, the meta-analysis also incorporates different kinds of SGLT2i, which creates some correlation between cost input and HR utilized.
The cost for SoC treatment is gathered from Sortsø et al. (2016), which, as stated above, has some limitations. Sortsø et al. (2016) do not specify which medications are incorporated within their cost, which is a limiting factor in this analysis [10]. Also, the current analysis does not consider the aspect of T2DM patients taking or adding more medications. SDC states that most T2DM patients take SGLT2i with their already insulin-regulating medication, which is most likely metformin. To avoid this limitation, the analysis needs to create a more detail-oriented rundown of the cost inputs within the model [68].

6.3.3 Utility

The current analysis estimates HSUVs for a population with comorbidities, extracted from Hvidberg et al. (2023) and the way to calculate it from Ara et al. (2017) [51], [55]. The current analysis utilizes the multiplicative methods from Ara et al. (2017) to combine T2DM HSUV with HF HSUV. However, Ara et al. (2017) state that two other methods exist to estimate the HSUV. The additive and minimum methods. The study states that the minimum method tends to overestimate HSUV, while both the multiplicative and additive methods tend to underestimate the HSUV [55]. Incorporating different HSUV methods to create a more nuanced analysis could be relevant for further analysis. This could be done by showing different ICERs calculated using other HSUV methods. Another approach could involve making random adjustments to the estimated HSUV values, like in the sensitivity analysis, and creating an upper and lower bound at 20% [55]. However, it is relevant to consider the number of comorbidities associated with a certain condition. The study by Hvidberg et al. (2023) states that T2DM patients, on average, have 5,8 comorbidities associated with them [51]. This does create a problematic approach to calculating an accurate

HSUV since Ara et al. (2017) state that estimating an HSUV for three or more comorbidities might create errors within the estimation of HSVU. Ara et al. (2017) state that the HSUV will quickly go towards zero by using the multiplicative method. However, more research is needed in this area to create a more correct assessment [55].

One study from the current research by Jafari et al. (2018) showed that if utility values were extracted from the literature search, the QALY values could have the potential for an over – or underestimation [39]. The current analysis is extracted from the literature search, and it may be beneficial to incorporate utility values based on the Thousand&2 study cohort to get a more precise measurement of utility values. However, it's also important to consider the aspect of which HRQoL is the most efficient in measuring T2DM ambulatory patients with HF. Two studies by Soriano et al. (2010) and Moser et al. (2009) measured HHF via SF-36 and Minnesota Living with Heart Failure Questionnaire (MLHFQ) [69], [70]. The exact correlation between their results and the current analysis is not ideal since they measure an actual population, whereas the current analysis considers a hypothetical scenario. However, this shows multiple ways of measuring HRQoL within HF populations, and it could be a relevant methodology to incorporate in further analysis.

6.4 Sensitivity

In the current analysis, a one-way DSA was conducted and visualized as a tornado plot with chosen parameters of interest. The tornado shows that the model is most sensitive to the costs associated with the health states 'Advanced HF' and 'HF'. This could indicate that minor changes regarding the health state costs can substantially impact the ICER.

However, this correlates with Bundgaard et al. (2016), which states that HHF is one of the costliest drivers within HF in Denmark [11]. Also, the paper done by the Heart Failure Policy Network states that HHF in Denmark is costly, and it will most likely be a cost-effective measure for reducing HHF [6]. This emphasizes the importance of accurate health state cost estimation within this Markov model.

The parameters with the least impact on the ICER were the uncertainty regarding the sensitivity and specificity of NT-proBNP at a cut-off of ≥ 400 pg/mL. This could indicate that some variation within these two parameters might marginal impact the ICER.

This means that costs associated with the health states are the primary factors driving the cost-effectiveness results, which might also be seen in the scenario analysis when utilizing an extreme cut-off at ≥ 2000 pg/mL, which has a high specificity (96,10%), meaning less T2DM patients will be going to the 'Advanced HF' health state, and thus making the NT-proBNP+SGLT2i arm

dominant. Having such a high specificity means there will be few false positives. However, the sensitivity is on the other spectrum, at 38,9 %, which means that the cut-off at ≥ 2000 pg/mL creates a lot of false negatives. This tells that NT-proBNP at that specific cut-off value fails to identify the number of truly false T2DM ambulatory patients with HF.

It is also important to note that parameters that lack a CI get an adjustment of 20 % or 50 % to their upper and lower bounds. This depends on how the parameters were sourced since the literature provided the parameters with a confidence interval. This highlights the need for a more accurate assessment, especially cost parameters, to create a precise DSA.

Considering the overall aspect of sensitivity analysis, it's clear that the current analysis lacks a probabilistic sensitivity analysis (PSA). A PSA is what's called a stochastic sensitivity analysis and is an analysis method that is based on distributions to look at the input parameters' uncertainties. Usually, a PSA follows what is called a 2nd order Monte Carlo simulation, which is specifically used for parameter uncertainty. The PSA has the potential to examine the combined impact of all the parameter uncertainties. Usually, the PSA will result in 10.000 iterations, presented on an ICE scatterplot and a cost-effectiveness acceptability course [65]. However, one of the main limitations regarding this current analysis is the available basic data. The data is not representative of both the population and patient setting. The model inputs are mainly sourced from grey literature to fit the Markov model, which creates a substantial lack of internal validity.

6.5 Scenario Analysis

The current analysis also conducted a scenario analysis to evaluate the impact of various NT-proBNP cut-off values and determine their influence on the ICER.

The results from both scenario analyses show that changing the NT-proBNP cut-off does impact costs, HHF, and QALY compared to the base-case scenario of ≥400 pg/mL.

The scenario analysis shows that at the extremely higher end of the NICE QALY threshold, the higher sensitivity and lower specificity at the ≥ 125 pg/mL cut-off lead to a higher cost but remain cost-effective. Yet, the ICER is close to being above the NICE QALY threshold of a fixed value of 20.000 pounds (174.600 DKK). However, it's important to note that these incorporated thresholds do not represent a Danish ambulatory care setting. The values are extracted from Taylor et al. (2023) [23], which utilizes an ESC-recommended cut-off for referral to echocardiography at ≥125 pg/mL for NT-proBNP and a higher NICE-recommended cut-off at ≥ 400 pg/mL, to get a referral to echocardiography. The Taylor et al. (2023) study uses these cut-off values as the diagnostic

performance of NT-proBNP within a primary care setting [23]. Taylor et al. (2023) state that the evidence available on a well-established cut-off value for NT-proBNP is scarce, and the current guidelines are based on small studies to create recommended cut-off values for NT-proBNP [23]. The DCS position paper also states that there aren't any clear cut-off values for NT-proBNP to diagnose HF accurately. The NT-proBNP concentrations used in the DCS position paper are only indicative indications, and there aren't any concise NT-proBNP cut-off values to diagnose HF. They are only seen as part of the diagnostic workup, without prominent high-risk markers [8].
The DCS position paper states that < 125 pg/mL can be used to rule out HF, which makes it relevant for the scenario analysis to consider a value above ≥ 125 pg/mL. The current analysis base-case scenario at ≥ 400 pg/mL does coincide with the DCS position paper, which states that values varying from 300 – 1799 pg/mL, depending on age, may indicate that the concentration is likely elevated [8]. The current research section in this analysis includes a study by Walkey et al. (2023). Walkey et al. (2023) state that it is recommended to incorporate an NT-proBNP cut-off with somewhat high specificity without sacrificing a reduction in sensitivity [36]. In an ideal state, this creates an accurate depiction of who is truly positive and negative. However, the DCS position paper uses the < 125 pg/mL as a rule out for HF, but if the assumptions are based on the sensitivity and specificity used in Taylor et al. (2023) [8], [23] the NT-proBNP cut-offs have a sensitivity at 94,6 % but a low specificity at 50 %. This does create a scenario where the DCS position paper will place a lot of HF patients in the category of being positive with HF. However, it cannot be highly specific about who is truly negative. This is why the utilization of a higher cut-off might be more beneficial for a more accurate diagnosis of HF within T2DM patients.

6.6 Perspective:

As seen in this current analysis, the health state 'Advanced HF' is one of the parameters with the most uncertainty regarding the ICER. The health state is defined as HHF, and the cost of hospitalization is prominently the main driver of this analysis.
Therefore, Denmark must improve HF screening and diagnosis in ambulatory and primary care. This current analysis and the current research section show that NT-proBNP is cost-effective and can avoid unnecessary referral to echocardiography. NT-proBNP can, therefore, also help to create a diagnosis in a timely matter and access treatment. All these factors are resourceful, and by creating a better understanding of the screening and diagnostic tool of NT-proBNP, the Danish healthcare system can save many of our scarce resources. However, reducing HHF does not only impact the

T2DM patients with HF, but it also has a bigger impact on the already overflown Danish hospitals. In today's Danish healthcare system, Danish patients can risk being on waiting lists for up to several years, with the combination of healthcare professionals who are working under a pressurized healthcare system, which creates a fear for the patient's safety. By utilizing NT-proBNP,+SGLT2i to create fewer HHF, it's possible to create a “de-hospitalization” scenario, in which the pressure is laid off, and the treatment of patients are either moved to specialized clinics or the patient’s own home [71].

Another perspective that could be interesting to incorporate when creating a scenario of “de-hospitalization” to the treatment in the patient's own homes is telemedicine. In Denmark, there is growing interest in the use of telemedicine for HF. Telemedicine can improve HF care for patients who have a hard time accessing specialized HF clinics. In Denmark, a study assessed telemedicine among Danish HF patients by creating patient-centered care around HF patients, their families, and healthcare professionals. Within health economics, the study shows a reduction in annual healthcare costs per person of 35 %, mainly due to a decrease in hospitalization [6].

6.7 Limitations:

The current analysis does encounter a lot of limitations, which hinder the internal validity of the analysis aim. The study was done firsthand, on relied data from the Thousand&2 study. However, the data wasn't available in time, and the current analysis relied on literature. This creates an uneven structure throughout the analysis since the population setting is based in a Danish context with certain characteristics from the Thousand&2 study. Still, most model input is based on studies whose results fit the Markov model best. The current analysis would have also benefitted from a study focusing on ambulatory settings regarding the sensitivity and specificity when screening with NT-proBNP. The DCS position paper does state some recommended guidelines to utilize to help with the diagnosis of HF [8]. However, the paper doesn’t provide sufficient Danish evidence that may benefit this analysis. However, it is important to note that Taylor et al. (2023) base their study on the ESC and NICE guidelines, which provide recommendations on an international level, which may help the overall diagnostic workup for the usage of NT-proBNP. However, the patient setting needs to be within ambulatory care since both the DCS position paper and Taylor et al. (2023) consider the primary care setting [8], [23].

The analysis could consider a deeper insight into the all-cause mortality rate for further investigation since the meta-analysis in the current analysis considers this. The HR for all-cause

mortality is primarily utilized within the transition probabilities for ‘HF’ to ‘dead’ health state. The analysis could implement some results regarding all-cause mortality and its impact on the cost and QALY it might induce.

7. Conclusion

This Markov model-based health economic evaluation shows that using an NT-proBNP cut-off value at ≥ 400 pg/mL makes the NT-proBNP+SGLT2i arm cost-effective when utilizing the NICE-recommended WTP threshold. Base-case results show that the incremental cost between the NT-proBNP+SGLT2i arm and the SoC arm is 1.503 DKK, keeping both arms cost-effective. Based on HHF, the NT-proBNP+SGLT2i arm indicates a lower HHF rate than the SoC arm. Based on the one-way DSA, the parameter cost for 'Advanced HF' shows the most uncertainty regarding the total cost per QALY ICER. The scenario analysis shows that an NT-proBNP cut-off ≥ 125 pg/mL creates a higher incremental cost between the NT-proBNP+SGLT2i arm and the SoC arm, with a higher ICER at 171.025, yet remains cost-effective. The scenario analysis shows an NT-proBNP cut-off ≥ 2000 pg/mL, with a considerably lower ICER at -147.507 DKK/QALY, making the NT-proBNP+SGLT2i arm more dominant compared to the SoC arm. Considering the WTP threshold, the incorporated model inputs, and assumptions regarding the Markov model, the annual screening with NT-proBNP and additional treatment with SGLT2i, compared to current diagnostic practice and treatment of HF in T2DM patients in a Danish Ambulatory care setting, is cost-effective, yet more expensive.

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Appendix A:

Table 13: Search string for the Current Research

	Search string	Hits
#1	"Health Care Economics and Organizations"[Mesh] OR "Health Care Economics and Organizations*"[tiab]	1,710,639
#2	"Cost-Effectiveness Analysis"[Mesh] OR "Cost-Effectiveness Analysis*"[tiab]	14,554
#3	(("Peptide Fragments"[Mesh]) OR "pro-brain natriuretic peptide (1-76)" [Supplementary Concept]) OR "Natriuretic Peptide, Brain"[Mesh] OR (("Peptide Fragments*"[tiab]) OR "pro-brain natriuretic peptide (1-76)" [Supplementary Concept]) OR "Natriuretic Peptide, Brain*"[tiab]	177,872
#4	Heart Failure"[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR "Heart Failure*"[tiab] OR "Heart Failure, Diastolic*"[tiab] OR "Heart Failure, Systolic*"[tiab]	267,241
#5	((("Health Care Economics and Organizations"[Mesh] OR "Health Care Economics and Organizations*"[tiab]) OR ("Cost-Effectiveness Analysis"[Mesh] OR "Cost-Effectiveness Analysis*"[tiab])) AND ((("Peptide Fragments"[Mesh]) OR "pro-brain natriuretic peptide (1-76)" [Supplementary Concept]) OR "Natriuretic Peptide, Brain"[Mesh] OR (("Peptide Fragments*"[tiab]) OR "pro-brain natriuretic peptide (1-76)" [Supplementary Concept]) OR "Natriuretic Peptide, Brain*"[tiab])) AND ("Heart Failure"[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR "Heart Failure*"[tiab] OR "Heart Failure, Diastolic*"[tiab] OR "Heart Failure, Systolic*"[tiab])	153

Appendix B:

Table 14: Transitions Tables for the SoC arm and NT-proBNP+SGLT2i arm

SoC	Transition to:				Check
Transition from:	Alive	HF	Advanced HF	Dead	Okay
Alive	0,954	0,0038	0,024	0,0183	1,00
HF	-	0,483	0,353	0,163	1,00
Advanced HF	-	0,400	0,250	0,350	1,00
Dead	-	-	-	1,000	1,00

NT-proBNP + SGLT2i	Transition to:				Check
Transition from:	Alive	HF	Advanced HF	Dead	Okay
Alive	0,926	0,0316	0,024	0,0183	1,00
HF	-	0,621	0,244	0,136	1,00
Advanced HF	-	0,400	0,250	0,350	1,00
Dead	-	-	-	1,000	1,00

SoC	Transition to:			
Transition from:	Alive	HF	Advanced HF	Dead
Alive	1-sum	HR_risk*symp_HF	p_A_AHF	p_A_D
HF	-	1-sum	p_HF_AHF	p_HF_D
Advanced HF	-	1-sum	p_AHF_AHF	p_AHF_D
Dead	-	-	-	1

NT-proBNP + SGLT2i	Transition to:			
Transition from:	Alive	HF	Advanced HF	Dead
Alive	1-sum	p_HF*NT_sens	p_A_AHF	p_A_D
HF	-	1-sum	p_HF_AHF*HR_HFH	p_HF_D*HR_M
Advanced HF	-	1-sum	p_AHF_AHF	p_AHF_D
Dead	-	-	-	1

Appendix C:

Table 15: Schematic overview of the annual health state costs [10], [11]

Annual Health State Costs

State	Assumptions	Costs (€)	Source
Alive	Secondary healthcare costs per person year	20.063,10	Sortsø et al. (2016)
Lower bound		16.050,477	+20%
Upper bound		24.075,715	-20%
HF	Secondary healthcare costs per person year	69.654,00	Sortsø et al. (2016)
Lower bound		55.723,198	+20%
Upper bound		83.584,797	-20%
Advanced HF	HF state cost and hospitalization due to HF	128.157,69	Sortsø et al. (2016) Bundsgaard et al. (2019)
Lower bound		102.526,150	+20%
Upper bound		153.789,225	-20%

Appendix D:

Table 16: Treatment and Diagnostic costs [10], [47], [48], [49], [50], [53]

SGLT2i costs

Type	Daily dose (mg)	Dose per year (mg)	Price per package (DKK)	mg per package (DKK)	Price per mg (DKK)	Price per year (DKK)	Source	
Dapagliflozin	10	3.652,50	467,70	280,00	1,67	6.100,98	Forxiga - DMA	pro.medicin
Empagliflozin	10	3.652,50	482,25	300,00	1,61	5.871,39	Jardiance - DMA	pro.medicin
Canagliflozin	100	36.525,00	462,10	3.000,00	0,15	5.626,07	Invokana - DMA	pro.medicin
						Average		
Base case value						5.866,15		
Lower bound						4.692,918		
Upper bound						7.039,376		

SoC costs

T2DM treatment cost (DKK)	T2DM+HF treatment cost (DKK)	Source
4641,35	9074,1	Sortsø et al. (2016)

HF treatment cost	DKK
Base case value	4.432,75
Lower bound	3.546,200
Upper bound	5.319,300

Diagnostic costs

Diagnostic tool	Cost (DKK)	Source
Echocardiography	2.026	DRG 05PR04
Lower bound	1620,8	
Upper bound	2.431,200	
NT-proBNP	264	Frederiksberg and
Lower bound	211,2	Bispebjerg hospital
Upper bound	316,8	

Appendix E:

Table 17: Health state Utility Values and the formulas incorporated.[51], [52], [55]

Observed values

State	Observed mean	Source
T2DM	0,752	
Heart Failure	0,678	
No history of T2DM or HF	0,974	Hvidbjerg et al. (2023)
No history of T2DM	0,917	
No history of HF	0,917	

Estimated HSUV for HF

Method	Estimated mean HSUV
Additive	0,570
Minimum	0,678
Multiplicative	0,591

HSUV - Advanced HF

	HSUV	Time-adjusted	Source
HFH	0,47	0,0129	Gu et al. 2020
HF	0,591	0,5744	
AHF	-	**0,5873**	

Methods used to estimate HSUVs for comorbidities	Source
Additive: UAdd, AB = U_nAnB - ((U_nA - U_A) + (U_nb - U_B))	
Minimum: U,Min, AB = min(U_nAnB, U_A,U_B)	
Multiplicative: U, Mult, AB = (U_nAnB * (U_A / U_nA) * (U_B / U_nB)	Ara et al.
Notes: U = Utility; AB - both condtion A and condition B; nA - not condition A; nB - not condition B; nAnB - neither condition A nor condition B)	

Appendix F:

Table 18: Search String for the Meta-analysis

	Search String	Hits
#1	Sodium-Glucose Transporter 2 Inhibitors[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "Sodium-Glucose Transporter 2 Inhibitors*"[tiab] OR "Sodium-Glucose Transporter 2*"[tiab]	7,258
#2	Heart Failure[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR "Heart Failure*"[tiab] OR "Heart Failure, Diastolic*"[tiab] OR "Heart Failure, Systolic*"[tiab]	268,011
#3	"Mortality"[Mesh] OR "Mortality*"[tiab]	1,299,655
#4	"Hospitalization"[Mesh] OR "Hospitalization*"[tiab]	440,346
#5	"Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus, Type 2*"[tiab]	181,684
#6	((((("Diabetes Mellitus, Type 2"[Mesh] OR "Diabetes Mellitus, Type 2*"[tiab]) AND ("Hospitalization"[Mesh] OR "Hospitalization*"[tiab])) AND ("Mortality"[Mesh] OR "Mortality*"[tiab])) AND ("Heart Failure"[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR "Heart Failure*"[tiab] OR "Heart Failure, Diastolic*"[tiab] OR "Heart Failure, Systolic*"[tiab])) AND ("Sodium-Glucose Transporter 2 Inhibitors"[Mesh] OR "Sodium-Glucose Transporter 2"[Mesh] OR "Sodium-Glucose Transporter 2 Inhibitors*"[tiab] OR "Sodium-Glucose Transporter 2*"[tiab])	259