Cost-Effectiveness Analysis of HealthB in Patients with Hypertension in Norway

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Master thesis

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Abstract

Objective

The aim of this thesis was to implement an economic evaluation to explore the potential cost-effectiveness of HealthB on blood pressure reduction and CVD risk prevention in Norway. Besides healthcare, societal costs were included to estimate the economic burden of hypertension and CVD.

Methods

A state transition Markov model was developed for three hypothetical groups of hypertensive patients, aged over 40 years, to estimate the QALY and LY gains of using HealthB. The time horizon of the model was lifetime years, with 1-year cycles. The baseline risk of CVD is based on population incidence rates. Data on the costs and utilities associated with events and states in the model were obtained from published sources. Deterministic and probabilistic sensitivity analyses were performed.

Results

From a healthcare perspective, HealthB is not cost-effective across three groups of hypertensive patients holding a WTP of 600,000 NOK/QALY. From a societal perspective, HealthB is cost-effective for grade 2 and 3 hypertensive patients holding the same WTP value.

Conclusion

HealthB in patients with hypertension generated more LYs and QALYs under the assumption of HealthB's effect on CVD prevention and of HealthB's cost. This thesis presented preliminary findings about the cost-effectiveness of HealthB. Further research is needed to evaluate the factual effect of HealthB when more clinical data are available.

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List of abbreviations

BP	Blood Pressure
CBA	Cost-Benefit Analysis
CEA	Cost-Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontier
CUA	Cost-Utility Analysis
CVD	Cardiovascular Disease
DRG	Diagnostic Related Groups
DSA	Deterministic Sensitivity Analysis
EQ-5D	EuroQol-5 Dimension
GP	General Practitioner
HIT	Health Information Technology
HL	Health Literacy
HRQoL	Health-Related Quality of Life
ICER	Incremental Cost-Effectiveness Ratio
IS	Ischemic stroke
LY	Life Year
MI	Myocardial Infarction
NICE	National institute for Health and Care Excellence

NMB	Net Monetary Benefit
NOK	Norwegian Kroner
NoMA	Norwegian Medicines Agency
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
SA	Sensitivity Analysis
WHO	World Health Organization
WTP	Willingness-To-Pay

1. Introduction

Hypertension is the most important risk factor for cardiovascular diseases (CVD), a leading cause of death and disability worldwide (Murray & Lopez, 1997). In 2014, around 30% of all deaths in Norway are caused by CVD(Ezzati et al., 2002). Nowadays, we can see an increasing trend in the number of hypertensives across the world. The number of adults aged 30–79 years with hypertension has increased from 650 million to 1.28 billion in the last thirty years across the whole world (WHO, 2021). Although the Tromsø survey demonstrates that Norwegians are showing a decreasing trend in average blood pressure for the last 40 years across all age groups (Bazilchuk, 2017), many Norwegians are still at a big risk of having hypertension. A study estimated that in Norway, approximately 750 000 persons of a total 5 million population aged from 45 to 74 years will fulfill the criteria for pharmacological agents for high blood pressure(Kjeldsen et al., 2019).

Uncontrolled hypertension is associated with acute cardiac events, such as myocardial infarction (MI) and ischemic stroke (IS)(Ulasi et al., 2011). Lowering blood pressure with effective antihypertensive medications can significantly decrease the risk of CVD(Psaty et al., 2003; Montgomery et al., 2003). Epidemiologic studies over the past 30 years demonstrated that good control of hypertension reduces the incidence and death rate of all stroke types dramatically, and it appears that all effective antihypertensive agents have similar efficacy to reduce stroke risk (Dubow & Fink, 2011). It is recommended that the first objective of treatment should be to lower blood pressure to < 140/90 mmHg in all patients < 80 years. In older patients (aged > 80 years) receiving BP-lowering drugs, it is recommended that systolic blood pressure should be targeted to a range of 140-150 mmHg(Williams et al., 2004) .

However, despite the wide use of efficacious antihypertensives in the reduction of blood pressure, only around 50 percent of people treated for hypertension are controlled to recommended levels(Kaambwa et al., 2014). Although several factors can explain the inadequate blood pressure control, patients' suboptimal adherence to the antihypertensive therapy has been cited as a major contributor to uncontrolled hypertension (Elliott, 2003).

Few new drugs are expected to arrive on the market in the next years(Suzanne & Roland, 2015), so the treatment of hypertension has to rely mostly on existing drugs. If we can't rely on new drugs to offset the adverse effect of nonadherence, promoting the effectiveness of the current

drugs by addressing non-adherence issues is necessary. Knowing the barriers which stop patients from following the treatment is an essential prerequisite to designing effective interventions that target these barriers and consequently promote adherence. Five factors, including demographic, socioeconomic, concomitant medical-behavioral conditions, therapy-related, healthcare team and system-related factors, and patient factors, are mainly contributing to nonadherence(Burnier & Egan, 2019), though we focus on the latter two factors in this study.

HealthB (Appendix 3) is an intervention considering healthcare team and patient factors. This intervention is a digital personal health platform designed to empower users to understand and communicate their health and achieve self-care. It is a horizontal platform that connects to different sources of information. Through self-registration and by adding external sources, such as a single disease or lifestyle application, vaccines, medical devices, test results, treatment plans, hospital journals, and public health data, one can own, understand, and communicate their health information. This platform enables people to own and understand their health data and together with healthcare providers create a personalized care plan to make users an active participant in their health and hence increase their quality of life. It allows people to keep a track of their health and share it with others to make users an active participant in their own health and increase their intrinsic motivation to live healthier.

There is no existing experimental data on the effectiveness of HealthB. Thus, an early cost-effectiveness analysis was developed to find the potential value of using HealthB alongside the standard of care for hypertension. The main question was: Is the use of HealthB cost-effective for the reduction of blood pressure and the prevention of CVD in Norway? Here, CVD was defined in the analysis as myocardial infarction (MI) and ischemic stroke (IS), which represent the largest, costliest, and most harmful aspects of the CVD burden(Stone et al., 2014). Cost-effectiveness will be determined on the basis of societal willingness-to-pay (WTP) thresholds(Briggs et al., 2006). Sub-questions were: (1) How large the effect has to be in order for HealthB to be cost-effective? (2) what price of Health should be set for it to be considered cost-effective? This study will be done in an explorative context, as there is still very little evidence available for the effects of this intervention.

HealthB is the intervention under consideration, while the standard of care is not a comparator because HealthB is not considered as an alternative to conventional treatment but considered as a supplement to common practice. Hence, a do-nothing comparator is chosen in the analysis.

This paper will consist of seven chapters including this one. The second chapter will be background, where information on hypertension, the definition of adherence, risk factors of adherence, and digital interventions to improve adherence will be provided. Chapter 3 will be about the theoretical aspects of economic evaluation. In chapter 4 the methods used to perform the evaluation will be stated. Chapter 5 will consist of the results from the analyses. Chapter 6 will be a discussion of the main findings, while the strengths and weaknesses of this study will also be discussed. The seventh chapter will be the conclusion of the whole thesis.

2. Background

2.1 Hypertension

Blood pressure is defined as the force exerted by circulating blood against the walls of the body's arteries. Hypertension is when the blood pressure is too high. A blood pressure reading is given in millimeters of mercury (mm Hg). It has two numbers. The first (systolic) number represents the pressure in blood vessels when the heart contracts or beats. The second (diastolic) number measures the pressure in the arteries between beats.

Hypertension is diagnosed if the systolic blood pressure readings on two different days are larger than 140 mmHg and/or the diastolic blood pressure readings on two different days are larger than 90 mmHg (WHO,2021).

2.2 Complications

Hypertension can cause serious damage to the heart. The higher the blood pressure and the longer it goes uncontrolled, the greater the damage. Excessive pressure on the artery walls can harden arteries, decreasing the flow of blood and oxygen to the heart. This elevated pressure and reduced blood flow can cause a heart attack(myocardial infarction). When the blood supply to the heart is blocked and heart muscle cells die from lack of oxygen, a myocardial infarction occurs. As the time for blood flow being blocked becomes longer, the damage to the heart becomes greater. Hypertension can also cause a stroke by blocking arteries that supply blood and oxygen to the brain. In addition, hypertension can cause kidney damage, leading to kidney failure(WHO,2021).

2.3 Current treatment

There are two well-established strategies to lower blood pressure: lifestyle interventions and drug treatment. Lifestyle considerations including diet, smoking cessation, and regular physical activity are fundamental to BP management and CVD prevention. Antihypertensive drugs are considered the first-line-of-defense in terms of pharmacological treatments, and most of them have been established as cost-effective and successful for BP reductions and the prevention of cardiac events. Patients with grade 1 hypertension who are not at high risk of hypertension-mediated organ damage are always recommended to take lifestyle interventions first. Patients

with grade 2 or 3 hypertension should receive antihypertensive drugs immediately in addition to lifestyle interventions.

2.4 Hypertension and adherence to antihypertensive drugs

The process of adherence to medications includes three major components according to a new taxonomy published in 2012(Kaambwa et al., 2014). These three components are initiation, implementation, and continuation of drug therapy. Thus, poor adherence can be explained as a failure to initiate pharmacotherapy, implement the dosing regimen, and persist in long-term therapy. Initiation does not start with a prescription but with the first dose of the medication to be taken. In clinical studies, 4% to 5% of patients never take their medication after prescriptions, despite the fact that they accepted to be enrolled in a study (Vrijens et al., 2008). The implementation of the dosing regimen can be easily explained in a way that medications are taken as often as prescribed. Poor implementation results in more or less prolonged periods of treatment interruptions, although the majority of patients omit their medications non-intentionally. Persistence is the length of time between the first dose of the medication taken and the last dose immediately preceding discontinuation. Non-persistence is one of the most common causes of poor adherence to hypertension. 50% of patients stop their treatment at 1 year (Vrijens et al., 2008), though patients who quit the drug therapy may not know hypertension should ideally be treated for life (Familoni et al., 2004).

Poor adherence to antihypertensive medication is a major contributor to inadequate blood pressure control (Poulter et al., 2020). Abegaz et al. (2017) have reviewed 25 articles that assessed the antihypertensive medication adherence and identified that 45.2% of the hypertensive patients are nonadherent to pharmacological agents and 83.7% of uncontrolled hypertensive patients were nonadherent to antihypertensives, while the proportion of nonadherence to the drug therapy is found to be 59.7% in controlled blood pressure patients. Their study also pointed out that nonadherence to drug therapies in hypertensive patients increases the risk of cardiovascular outcomes. Similarly, a study by Poulter et al. (2020) found that adherence to antihypertensive treatment not only has a considerable impact on the control of blood pressure but on cardiovascular morbidity and mortality. They pointed out that compared to patients with medium or low adherence, patients with high adherence were 45% more possible to achieve blood pressure control. They mentioned observational data from the Lombardy region which demonstrated that adherence to antihypertensive drug therapy reduced the risk of CVD events by 37 percent (Corrao et al., 2011).

2.5 Adherence and patient factor

As mentioned before, several categories of factors are associated with nonadherence. As noted in 2003 WHO Report on adherence, patient-related factors are often the principal focus of efforts to understand and improve adherence(santé & Organization, 2003). A lack of knowledge about hypertension among patients may cause suboptimal results and inappropriate health decisions made by them. For example, some patients do not accept the diagnosis, some of them perceive prescription medications as ineffective in controlling hypertension or likely to have major adverse effects, and others may ignore the potential severity of a currently symptomless disease on future health risks, including life-threatening conditions(Burnier & Egan, 2019). These situations are obviously an impediment to adherence and consequently affect blood pressure control. Hence, education to improve health literacy in hypertensive patients is often a component of several multimethod interventions.

Health literacy is the ability that individuals have to obtain, process, understand, and use health information to make appropriate or informed health decisions. It can be applied across three domains including healthcare, disease prevention, and health promotion (Sørensen et al., 2012; Sørensen et al., 2015). Health literacy has become more and more important for patients in the era of the internet since there is a large amount of new health information including some factually incorrect information on the Internet every day. Patients who lack health literacy may have difficulties in processing and applying information relevant to health. As a result, patients are likely to make inappropriate health decisions according to misleading or deceptive information. However, if patients have enough knowledge to deal with health information, they can enjoy a substantial benefit. For example, amidst the COVID-19 pandemic, individuals who possess health literacies positively skew the spread of the disease by finding and applying information related to the coronavirus(Okan et al., 2022).

High levels of health literacy are needed for hypertensive patients to acquire health information and properly comply with medical personnel advice. There are studies conducted to find the relationship between health literacy, adherence, and hypertension treatment control. Darvishpour et al. (2016) conducted a descriptive cross-sectional study on 257 patients with hypertension. They found that health literacy was significantly related to monthly hypertension control and education programs provided to patients with poor health literacy can have a major role in promoting community health. Patients with adequate health literacy were more successful in the control and treatment of their diseases because adequate health literacy skills

of patients caused a higher rate of adherence to their medical regimens(Ingram, 2010). Kalichman et al. (1999)found that patients with low health literacy levels expressed their difficulty to understand and act upon health information resulting in nonadherence to medical instructions.

2.6 Adherence and healthcare team factor

When looking at adherence from a more practical side and from the practitioner's perspective, the patient-provider relationship is a key element to improve adherence level(Poulter et al., 2020). The quality of the interaction between the patient and healthcare provider, the communication style of providers, and patients' participation in treatment decisions all impact adherences (Hill et al., 2011;Burnier, 2017) .Trust in healthcare is critical. If patients have no confidence in their doctors' competency, they will not accept the diagnosis and treatment decisions made by this doctor. A highly qualitative interaction and collaborative communication style will also help build trust between providers and patients. For example, care providers with a collaborative communication style may ask 'are you having any problems with your medications such as they're too costly or cause unpleasant adverse effects?' rather than 'did you take your medication?' This way can help patients trust their doctors and participate in treatment decisions. Participation in decisions on what medications to take makes patients more adherent than little engagement in the decision(Roumie et al., 2011). There is a study demonstrating that a lower adherence in racial-ethnic minorities may be because they are less often engaged in decisions on their treatment than white adults(Ratanawongsa et al., 2010).

2.7 Health information technology and HealthB

Recent guidelines have emphasized the important need to address drug adherence as a major issue in hypertension management(Burnier & Egan, 2019). With the development of information technology, the use of it in health as an efficient and low-cost measure to address non-adherence is gradually increasing. During the 2021 World Health Summit, it was emphasized by Marelize Gorgens of the World Bank that digital health services are not second-tier forms of healthcare but first-tier forms of healthcare(World Health Summit, 2021).

In patients at high risk for major adverse cardiovascular outcomes, electronic monitoring tools are used for detecting nonadherence and for improving adherence(Burnier & Egan, 2019). This monitoring device contains a supply of medication and an electronic chip that records the

removal of a dose from the container. Although it is a reliable technique to diagnose poor adherence and to support adherence in chronic treatments, it does not solve the root cause behind non-adherence. This monitoring tool reminds patients to take medicines and records non-adherence, but patients can pretend to take medication by opening the box and discontinue drug therapy if they do not accept this drug therapy due to a lack of understanding of hypertension and poor interaction with care providers.

HealthB intervention is a type of health information technology (HIT) intervention and is still under development. It allows users to easily collect, understand and communicate their health information in a way a physician or other care deliverer understands. It is not specially designed for hypertensive patients, but its characteristics may have a positive impact on blood pressure management. For example, patients can have a deeper understanding of hypertension through different sources of information on HealthB. They can also share their health information with other users, patients and care personnel and communicate with them. Care providers can make use of this platform to improve the communication quality with patients, which in turn will motivate patients to better comprehend and participate in their treatment plans.

There are several studies about the effect of health literacy and/ or providers' engagement interventions on blood pressure. Albini et al. (2016) conducted a pilot study to evaluate whether ICT and mobile health tools can improve blood pressure control by increasing patients' health literacies and by enhancing care providers' engagement. The conclusion suggests that ICT and mobile-based health tools have a positive effect on hypertension management and patients' adherence. Another paper from Miller (2016) has used meta-analytic methods to suggest the relationship between health literacy, health literacy interventions and treatment adherence. A total of 220 published articles were included. The result was that health literacy was positively associated with adherence. Moreover, this study suggested that health literacy interventions increased both health literacy and adherence outcomes. Although the actual effect of HealthB on blood pressure is uncertain, it is still of interest to develop an early CEA to evaluate the potential value of this intervention.

3. Theoretical Framework

3.1 Economic Evaluation in Healthcare

Economic evaluation in healthcare is a systematic approach to collecting data and assessing the costs and outcomes of various healthcare technologies or health strategies. A full economic evaluation involves a comparison between two or more alternative technologies, and this evaluation considers both the consequences and costs. Generally, this assessment is conducted through decision analytic models. Since healthcare resources (i.e., equipment and personnel) are scarce, it is necessary to allocate resources effectively to the optimal healthcare technologies. Economic evaluation in healthcare can satisfy the need for decision-maker to distribute resources among competing needs. For example, the cost-effectiveness of a new intervention can be evaluated to be compared with a comparator (a do-nothing comparator if an intervention is entirely new or the current standard of care) under conditions of uncertainty. Economic evaluation tries to accurately estimate the trade-off between costs and effects of the choices being considered within healthcare and to explicitly estimate the opportunity cost of choosing one choice over another (Briggs, Claxton & Sculpher, 2006; Drummond et al., 2015).

There are three categories of economic evaluations: cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs) and cost-benefit analyses (CBAs). The common point between these methods is that costs are measured in monetary units for all of them, while the distinction between them is that the outcomes are measured in different terms (Drummond et al., 2015).

3.2 Cost-Effectiveness Analysis

This type of analysis measures costs in monetary units, while it measures effects in a natural unit. Such units can include gains in life years, change in mmHg blood pressure measurement or the reduction of years lived with the disease, etc. The best alternative intervention would be the one that yields the most effects, though not necessarily the least costs, as long as the effects outweigh the costs (Drummond et al., 2015). Compared to other types of analyses, CEA is relatively easy to undertake, and it is most useful in evaluating alternative approaches with the same outcome measure because of the natural units used in effect measurement. However, a limitation is that comparing these analyses with interventions from other programs that measure with different outcome units is challenging, so CEA is not applicable if it is used to compare the benefits of new interventions with the loss of any existing programs (Drummond et al., 2015).

3.3 Cost-Utility Analysis

CUAs are often referred to as a variant of CEAs. The mere difference is that effectiveness in this type of economic evaluation is adjusted to reflect the impact of the outcome on the subjective well-being of the individual. The quality-adjusted life year (QALY), including both the quality and the quantity of life lived, adopts quality weights that are based on utilities for health states and may vary across individuals or groups of individuals. QALYs gained describe the change in utility value induced by the treatment (Drummond et al., 2015). The QALY can range from a value between 0 (death) and 1 (perfect health). The QALY is calculated through the utility values, which can be measured through direct and indirect methods. The main direct methods are the visual analog scale, standard gamble method, and time-trade off. The main indirect methods are questionnaires (i.e., the Health Utilities Index (HUI), EQ-5D from the EuroQoL Group, and the Short Form 6D) (Drummond et al., 2015). The health-related quality of life (HRQoL) can be elicited out of the methods mentioned above. HRQoL, represented by quality weights, reflects a multidimensional concept that includes physical, mental, emotional, functional and social well-being depending on the state of health (Yin et al., 2016). It is calculated by multiplying the duration of time spent in a health state by the HRQoL weight (i.e. utility score) associated with that health state.

An advantage of the CUA is that, unlike CEA, it allows for comparison with interventions from other programs. The QALYs provide consistency not only when comparing groups of patients with different diseases but when comparing health gained with the health expected to be lost elsewhere as a consequence of additional healthcare costs. Several economic evaluation guidelines, set by national governmental organs, prefer a cost-utility analysis as it enables comparison between programs. Nevertheless, there are countries that view QALYs as a biased effect outcome, as it is not always the individual patient that reflects their personal experience but rather the general public. This remains an ongoing discussion (Drummond et al., 2015).

3.4 Cost-Benefit Analysis

This type of analysis measures both costs and outcomes in monetary units. CEAs and CUAs are methods to research the best allocation of an existing budget, but do not provide information on whether it is worthwhile to expand the current budget. A cost-benefit analysis (CBA) does provide this information. Additionally, as with the CUA, effects and outcomes can be compared with interventions in other public programs as they are represented in monetary

terms. Results of the CBA can be shown by the net benefit, which is the difference between the benefit and costs of each intervention compared. It is acceptable when the net benefit is larger than zero. However, CBA is a popular type of evaluation in many fields, but less common in health economic evaluation as it is challenging to assess health outcomes in monetary values (Drummond et al., 2015; York Health Economics Consortium, 2016).

3.5 Early cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is traditionally used to provide decision support in the implementation phase of new or current health technology(Kristensen et al., 2009). An early CEA is to evaluate interventions still in development and it may be able to help decision makers examine the medical, economic, social, and ethical implications of a health intervention to determine the potential of its incremental value in health care(Støme et al., 2019).

Currently, little specific guidance on how to perform early CEAs of medical tests exists. A guideline introduced by Buisman et al. (2016) suggested possible steps taken in an early CEA. The late, or usual, CEA steps are based on the Diagnostic Assessment Program (DAP) Manual from NICE (National Institute for Health and Care Excellence) guidelines (Buisman et al., 2016), which are widely used across Europe when conducting economic evaluations (Briggs et al., 2006).

In the early CEA, one starts with narrowing down the scope of the research (i.e., patient population, intervention, and comparator), followed by a synthesis of evidence on current test strategies, and then modeling outcomes and cost-effectiveness. This process is similar to a late or usual CEA. However, the difference between these two methods is that in the early CEA, less or no clinical data is available leading to more exploratory analysis and the final decision involves continuing test development, rather than making a reimbursement decision. Thus, the early CEA evaluates the potential cost-effectiveness of a new strategy rather than the actual cost-effectiveness when clinical data is available in the late CEA.

3.6 Perspective in Economic Evaluation

What type of costs should be taken into consideration depends on the chosen perspective of the study. The perspective used in an economic evaluation is often determined by governments through national guidelines for economic evaluation. The perspectives include individual patient perspective, institutional perspective, governmental payer perspective and societal

perspective (Drummond et al., 2015). The difference between the perspectives is that the costs included in each perspective are different. All possible costs that affect the societal and healthcare sector are included from the societal perspective. For example, the cost of hospitalization, medication, and staff, productivity loss, informal care costs, travel costs, and administration costs are all considered in this perspective. The healthcare or insurance company perspective, however, includes costs that only relate to the healthcare sector, such as inpatient care and outpatient care.

3.7 Decision-Analytic Modelling

A decision analytic model can bring different sources of data together to analyze a specific problem(Drummond et al., 2015). Decision-analytic modeling is a systematic approach in which a model is created using mathematical and statistical relationships between parameters to define possible outcomes of different alternatives under uncertainty (Briggs et al., 2006). A firm understanding of the decision problem and the clinical characteristics of the health problem in question is vital during the process of selecting and building a decision-analytic model (Roberts et al., 2012). There are several types of decision-analytic models, including decision trees, Markov models, Microsimulation models, Dynamic models, and Discrete event simulation models (Kuntz et al., 2013). Various models have various characteristics, but they have in common that they all use probabilities to reflect the likelihood of events or changes in health conditions, and the expected values to inform decision maker. Although all of them have different characteristics and are suited to different types of decision problems, the Markov model is one of the most widely used models (Drummond et al., 2015). It is suitable for long-term diseases, such as chronic diseases, and can reflect the disease's progress (Drummond et al., 2015). The model is based on a series of mutually exclusive states that can represent possible progress. A patient can transition between states within the model several times. An important assumption in this model is that future states are only relying upon the current state. Once a patient enters a state, all patients are considered to be homogenous regardless of past events(Briggs et al., 2006).

The length of stay within a cycle depends on the disease progression and the effect of the intervention. The event rates of patients in a given state in a given cycle are converted into transition probabilities for the Markov model according to methods described by Briggs et al (2006). Equations(1) used for converting rates into probabilities and vice versa were as follows, where p is the probability, r is the rate, and t is the time period:

$$p = 1 - \exp(-rt)$$
$$r = -[\ln(1 - P)]\,/t \quad (1)$$

Risks were cataloged and maintained as incidence rates to allow for efficient implementation of relative risk adjustments. Incidence rates were transformed into probabilities within the model itself when calculating transition probabilities between cells and cycles.

A Markov model assumes all events take place at either the start or the end of a cycle. However, in reality, a transition can occur at any point in time. No correction may lead to an over-or underestimation of the accumulated costs and outcomes in the model. Therefore, a half-cycle correction is applied to correct the underestimation or overestimation. The half-cycle correction equation is presented in Equation (2), in which A is total costs or total utility and C is the cost or utility in one cycle (Drummond, 2015).

$$A = \frac{1}{2} \times C_1 + C_2 \ + \cdots + C_{64} + \frac{1}{2} \times C_{65} \quad (2)$$

3.8 Sensitivity Analysis

As mentioned, early CEAs are surrounded by uncertainty since they are often conducted without the support of trial-based data. When the uncertainty is not properly accounted for, this can cause a risk of wrong decision making (Briggs et al., 2006). For these analyses especially, the model needs to be thoroughly assessed regarding uncertain data.

Sensitivity analysis was to deal with uncertainty in the interpretation of results and to test the impact of different implementation strategies when the technology is still dynamic. There are two main types of sensitivity analyses: deterministic and probabilistic sensitivity analysis (Drummond et al., 2015).

Deterministic sensitivity analysis methods assess the isolated effect of one parameter on the model result. One-way sensitivity analysis was performed by selectively adjusting one parameter and then comparing the effects of this adjustment with the main deterministic results. However, in two-way sensitivity analysis, two parameters are adjusted at a time while others

are fixed (York Health Economics Consortium, 2016). The deterministic sensitivity analysis (DSA) can be useful to see the effect of changing one specific parameter or a set of parameters on the ICER. However, because of the complex interactions between parameters present in many decision-analytic models, deterministic analyses are not sufficient to reflect the combined effect of the uncertainty from all parameters(Drummond et al., 2015).

Probabilistic Sensitivity Analysis(PSA) is a solution to measure the combined effect of the total parameter uncertainty. PSA assigns a distribution to all parameters, where distributions of mean values replace single point estimates. This can make the PSA more explicit. The characteristics of the parameter determine the distribution (Drummond et al., 2015). For example, probabilities and utility always use Beta distributions, while costs always use Gamma distributions. Monte Carlo simulation was performed in which the model was simulated 1000 times using the random draws for each input parameter according to its respective distribution.

The results from the PSA are recorded and analyzed within the net benefits framework, and are visualized in the cost-effectiveness acceptability curves (CEAC) and cost-effectiveness acceptability frontier (CEAF). A CEAC gives the probability of an intervention being cost-effective given several cost-effectiveness thresholds. The probability varies from 0 and 1. Zero indicates that the intervention is impossible to be cost-effective, while one indicates that the intervention is 100 percent of being cost-effective.

The CEAF is closely correlated to the CEAC. As the CEAC, the CEAF also summarizes the uncertainty on the result of an economic evaluation by indicating which treatment is cost-effective at different threshold values. Unlike CEAC, the CEAF displays different “switch points” at which an intervention is more cost- effective than a previous intervention. When three or more interventions are being compared together, CEAF is useful to visualize the points at which the cost-effectiveness changes from one treatment to another (Drummond 2015; Briggs et al., 2006).

4. Methods

4.1 Thesis object

This thesis aimed to develop a state-transition Markov model in Microsoft Excel and to evaluate the potential cost-effectiveness of a personal digital healthcare platform (HealthB) for reducing the risk of cardiovascular disease based on HealthB's effect on high blood pressure in Norway.

4.2 Hypothesis

Since there is no available trial-based data on how HealthB influences health literacy and care providers' engagement with patients and how the latter two influence adherence and blood pressure, it is assumed that HealthB has a positive effect on health literacy and care providers' engagement and consequently improve patients' adherence to antihypertensive medications and causes a reduction in blood pressure. Because of the same reason, it is assumed that HealthB will cause an average systolic pressure reduction of 10 mmHg for each patient in the cohort due to the improvement of health literacy and adherence. Most analyses were performed on this hypothesis. Two-way sensitivity analysis incorporated estimated relative risk reductions of MI and IS events. This sensitivity analysis was developed to explore the results with different relative risk reductions and to partly answer the question that how large should the effect of HeathB be in order for this intervention being cost-effective.

4.3 Decision Analytic Modeling

Since HealthB is still in development, early CEA was used to estimate the potential future value of this intervention in the thesis. Data was collected from literature, stakeholders, and experts to build scenarios to show the potential value of HealthB.

A state-transition Markov model was developed to model the transition rate from hypertension to MI and IS as well as death. The model estimates the incidence of CVD specifically within the Norwegian population. Individuals who have hypertension are at risk of experiencing first-ever CVD events. Those who survive these events transition into chronic post-CVD health states, where they remain at heightened risk for further events or death. Normally, these individuals may still be at very high risk for CVD due to other factors, but high blood pressure is the only factor considered in this study. All events and states can cause death directly. Each

cycle length is one year and only one CVD event is possible per cycle. This means that a patient cannot suffer MI and IS in the same cycle. A cohort of patients can begin the model at any age from 40 years upward. The model runs up to age 100 or until everyone is dead. Men and women are modeled in combined cohorts. HealthB is assumed to reduce the relative risk of CVD due to a reduction of blood pressure – this is, the transition rate from hypertension to CVD will be decreasing and a smaller number of patients will move to CVD states. A more detailed technical description of the model and its parameters is available in Appendix 1.

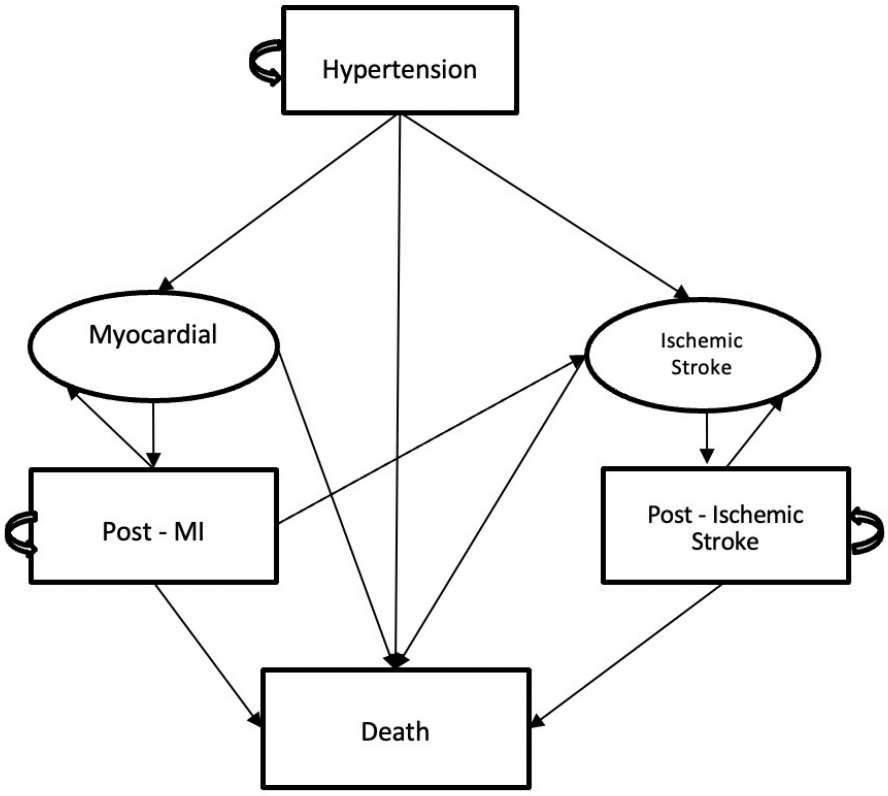

Figure1. Ovals represent events while rectangles represent health states. Looped arrows indicate a patient can remain in a health state for more than one cycle. Patients can be in only one health state per cycle.

4.4 Population

A hypothetical cohort of 1000 patients was used for this analysis. On one hand, this thesis mainly focused on the effect of hypertension control on the risk of MI and IS through HealthB. On the other hand, the incidence and prevalence rates of hypertension are higher in the age group of 40 years and above. Therefore, the target population for this study was patients over

40 years old with hypertension. They were modeled from 40 until 100 years old. In addition, hypertension is recommended to be classified as grade 1 hypertension with SBP 140-159 mmHg and/or DBP 90-99 mmHg, grade 2 hypertension with SBP 160-179 mmHg and/or DBP 100-109 mmHg, and grade 3 hypertension with SBP ≥ 180 mmHg and/or DBP ≥ 110 mmHg(Albini et al., 2016). Moreover, different grade of hypertension has different transition rate to CVD. Hence, three cohorts were developed: cohort only with grade 1 hypertension, cohort only with grade 2 hypertension, and cohort only with grade 3 hypertension.

4.5 Perspective

A healthcare payer and societal perspective were chosen for this analysis. A healthcare perspective was chosen according to the Norwegian guidelines for single technology assessments(NoMA, 2018). HealthB is not a medical device with the current form of the platform, but it will be classified as a medical device once the platform offers features such as health literacy and integration with third parties. In this study, HealthB was assumed to be a medical device, so the cost of HealthB was included in costs from a healthcare perspective. A societal perspective included was because Norway is considering changing guidelines to a societal perspective and the real reason behind this is that it's representing reality better. For instance, production loss will fall outside of the healthcare sector from a healthcare perspective, but sometimes this loss is very big and has an impact on the conclusion about the intervention's cost-effectiveness. From a health care payer perspective, the focus is on direct medical costs, which included all those associated with treating hypertension, MI, IS, and post-CVD health states. Production loss is included in a societal perspective. All costs were half-cycle corrected and were calculated for one year.

4.6 Time Horizon

The blood pressure reduction and prevention of CVD risk is a question of long-term risk reduction. The effect of HealthB on blood pressure is supposed to be not evident for several weeks and the prevention of cardiac events is only clear over many years of consideration. Moreover, the cost of treatment for hypertension and CVD must be considered from a lifelong perspective in order to accurately capture the true costs incurred by and reduced by HealthB. Hence, a lifetime horizon was chosen for this analysis.

4.7 Outcomes

The health outcome of this analysis is measured by the QALYs and life years (LY). Cost-effectiveness outcomes are presented as the incremental cost per unit of effectiveness, known as the incremental cost-effectiveness ratio (ICER). The ICER, shown in the equation (3), is the ratio of incremental costs(C) and effects(E) of the compared alternatives (b = intervention and a = comparator):

$$ICER = \frac{Incremental\ cost\ of\ an\ intervention}{Incremental\ effect\ of\ an\ imtervention} = \frac{Cb - Ca}{Eb - Ea} = \frac{\Delta Costs}{\Delta Effects} \quad (3)$$

The ICER can have a positive or negative outcome. A negative ICER may reflect both cost savings and negative health outcomes. These are very opposite outcomes and a conclusion can't be made merely based on this ICER. Thus, in the case of a negative ICER, it is best to use the net monetary benefit (NMB), which is calculated by multiplying the WTP threshold (λ) by the incremental effect (ΔE), from which the incremental cost(ΔC) is subtracted. The WTP entails how much the society is willing to spend on a certain service or good.

$$NMB = \lambda * \Delta E - \Delta C > 0 \quad (4)$$

This process can be performed from any given perspective. If the value of the incremental NMB is larger than 0, the intervention is preferred over the comparator. If the value of the NMB is lower than 0, the comparator is preferred over the intervention. An ΔNMB of 0 implies there is no difference to choose between the comparator and intervention because the cost-effectiveness is the same.

Borderline Cost-Effectiveness

Although the 600,000 NOK willingness to pay (WTP) threshold per additional QALY gained is widely used in Norwegian economic evaluations, it is an unofficial guideline rather than a strict rule. Because treatments with ICERs higher than this are often approved for reimbursement in Norway (Dagens Medicin, n.d.), this study will consider treatments with ICERs between 600,000 and 700,000 NOK/QALY to be borderline cost-effective. A recent review of decisions made by the Norwegian Medicines Agency confirms that a Norwegian threshold for drugs is likely in the range of 600,000 and 700,000 NOK/QALY(Dagens Medicin, n.d.). In the Norwegian healthcare system, an ICER is the main measurement of an intervention, and ICERs under a threshold value are considered acceptably cost-effective. Therefore, if we

hold a strict 600,000 NOK/QALY threshold without indicating borderline ICERs, it does not conform with real-world leniency.

4.8 Discount Rate

Both costs and utilities were half-cycle corrected and discounted at a rate of 4%, as suggested by the Norwegian Ministry of Finance(Wisløff, 2008).

4.9 Measurement of Effectiveness

Given the fact that HealthB is in development and this study was conducted without trial-based data, there is a lack of information regarding the reduction of blood pressure and the prevention of cardiovascular disease as a direct result of HealthB. The effect of HealthB on the prevention of cardiovascular disease was modeled through a hypothetical relative risk reduction due to the blood pressure reduction. It is already assumed that HealthB will cause an average systolic pressure reduction of 10 mmHg, so relative risk reductions were calculated based on the evidence from a recent meta-analysis that a 10mm Hg reduction in systolic BP in hypertensive patients reduces the risk of major CVD events by 20%, CHDs by 17%, stroke by 27%, heart failure by 28%, and all-cause mortality by 13%(Ettehad et al., 2016), though these estimations of relative risk have wide confidence intervals due to limited data resources. The relative risk of MI events when a hypertensive patient reduces 10 units of systolic blood pressure was estimated to be 0,8 and the relative risk of IS events was estimated to be 0,73(Table1). Here, the risk reduction data for major CVDs was used to calculate data for MI. Modeling the effect of HealthB through the relative risk estimates of this meta-analysis is an alternative before more data becomes available.

Table1. Key Treatment Effect Parameters

Relative Risks (every 10 mmHg BP reduction)	RR	(SE)	Source
MI event	0.80	(0.16)	(Abegaz et al., 2017)
IS event Abegaz et al.,	0.73	(0.15)	(Abegaz et al., 2017)
All-cause mortality	0.87	(0.17)	(Abegaz et al., 2017)

Table1. The assumed relative risk of CVD and all-cause death rate after using HealthB with 10 mmHg of blood pressure reduced.

The utility of the model is primarily measured through the Quality Adjusted Life Year (QALY). QALYs which combine length and HRQoL into a single generalized measure, allow for comparisons of effectiveness both within and across various treatments (Briggs et al., 2006). This report combines QALY estimates from different papers and analyses. Most of them use the EQ-5D HRQoL questionnaire and Time-Trade-Off (TTO) methods. QALY values are assigned to hypertension with non-CVD states and all chronic CVD states (Table 2). Most QALYs used in this model are calculated from EQ-5D results according to the commonly used UK index tariff, which was used for all values to help maintain consistency across QALY estimates(Augestad et al., 2012).

Table2. Key Utility Parameters			
CVD Utilities	Value(QALYs)	(SE)	Source
MI event	0.71	(0.08)	(Wisløff et al., 2014)
Post-MI	0.8	(0.2)	(Pettersen et al., 2008)
IS	0.74	(0.25)	(Luengo-Fernandez et al., 2013)
Post-IS (40-75)	0.68	(0.25)	(Luengo-Fernandez et al., 2013)
Post-IS (75+)	0.63	(0.25)	(Luengo-Fernandez et al., 2013)
Age-Specific Utilities for patients with hypertension			
40-49	0.86	(0.17)	(Maniadakis et al., 2011)
50-59	0.83	(0.17)	(Maniadakis et al., 2011)
60-69	0.81	(0.16)	(Maniadakis et al., 2011)
70-79	0.80	(0.16)	(Maniadakis et al., 2011)
80+	0.74	(0.15)	(Maniadakis et al., 2011)

Table 2. QALY values for CVD events, Post-CVD states, and age-specific QALYs for hypertensive patients without a history of CVD.

4.10 Estimating Resource Use and Costs

Estimating costs in model-based economic evaluation is a process of estimating resource use for all relevant states, events, and treatments, and then assigning accurate unit costs to each resource (Husereau et al., 2013). The cost of hypertension treatment mainly includes three

components: cost of drug therapy, cost of GP visits, and cost of blood tests. The components of this cost are based on NICE guidelines for hypertension. Most estimations for resource-use of CVD events and post-CVD states are made according to methods described in the NorCaD model (Wisløff, 2008). NorCaD costs are well-validated and are frequently cited in Norwegian economic evaluations and health technology assessments (Wisløff et al., 2014).

Unit cost components include the cost of drugs, fees for GP visits, and mean cost-reimbursement for diagnosis-related groups. Unit costs are taken from publicly available information including the Norwegian Directorate of Health (DRGs), the Normal Price Schedule for GPs and Emergency Care, and the Norwegian Medicines Agency and Norwegian Prescription Database (Legemiddelverk, n.d.; Innsatsstyrt finansiering, n.d.; Normaltariff, n.d.; Norwegian Prescription Database, n.d.). The average unit cost of drugs is taken from the Norwegian Medicines Agency. When multiple drugs are available within a given class, average drug costs were reflected by the cost of the most prescribed drug, which could be identified through the Norwegian Directorate of Health's report on Drug Consumption in Norway (Legemiddelforbruket, n.d.).

HealthB is currently under development and its pricing is not finally settled, so the cost of it will be changing. The yearly price was temporarily assumed in this model as 10,000 NOK and was assumed to remain unchanged over a lifetime in the model. The cost can be easily calculated for a patient who uses HealthB: 10,000 NOK for one year, 100,000NOK for ten years, and 600,000 NOK for lifetime use. It was also assumed that cost of HealthB is the same for three groups of the population. To adjust the uncertainty surrounding the cost of HealthB, a one-way sensitivity analysis was used later.

Table3. Key Cost Parameters (all costs 2022 Norwegian Kroner)

Costs	Value(NOK)	Source
Cost of Stroke (event)	248,612	(Wisløff, 2008 ;Wisløff et al., 2014)
Post-IS(40-75)	138,761	(Wisløff, 2008 ;Wisløff et al., 2014)
Post-IS 75+	264,543	(Wisløff, 2008 ;Wisløff et al., 2014)
Cost of MI (event)	207,630	(Wisløff, 2008)
Post-MI	4,007	(Wisløff, 2008)
Grade 1 hypertension	1855	(Legemiddelforbruket, n.d.; Legemiddelverk, n.d.)
Grade 2 hypertension	6533	(Legemiddelforbruket, n.d.;

		Legemiddelverk, n.d.)
Grade 3 hypertension	9526	(Legemiddelforbruket, n.d.; Legemiddelverk, n.d.)
HealthB	10,000	

Table 3. Total cost per year estimates for CVD events, post-CVD states, different grades of hypertension, and HealthB.

Total costs from a societal perspective included direct medical costs associated with treating and preventing hypertension and CVD and a production loss as a result of cardiac events. It was assumed that a proportion of patients with moderate or severe stroke could not return to work, but other patients could work again. Hence, the annual unemployment patients in the cohort were calculated by multiplying the number of alive patients without moderate or severe stroke with the age-specific workforce participation rate. All costs are total costs per year for states or events. More details on cost components are modeled and given in Appendix 1.

Table 4. Cost parameters related to production loss		
Parameter	Value	Source
Average Annual Wage (NOK)	650,000	(Statistics Norway, n.d.)
Payroll Tax	0.084	(Statistics Norway, n.d.)
Production Loss per person (NOK) = (Wage* (1-tax))	595,400	(Statistics Norway, n.d.)
Proportion Employed (40-54)	0.868	(OECD, n.d.)
Proportion Employed (55-64)	0.731	(OECD, n.d.)
Proportion Employed (65-69)	0.279	(OECD, n.d.)
Proportion Employed (70-74)	0.071	(OECD, n.d.)
Proportion Employed (75+)	0	
Prob. Moderate or Severe Stroke (<75)	0.4	(Wisløff, 2008 ;Wisløff et al., 2014)
Prob. Moderate or Severe Stroke (75+)	0.68	(Wisløff, 2008 ;Wisløff et al., 2014)

Table 4. Cost parameters related to production loss. Labor force participation rate for people aged over 75 was assumed to be 0.

4.11 Transition probabilities

Transition probabilities from a different grade of hypertension to MI or IS were calculated by multiplying relative risk with incidence rates first and then using the conversion model given by Briggs et al. (2006). Relative risk is increasing as a function of blood pressure. This model used gender-combined and age-specific incidence rates. The latter was taken from publicly

available population registry data. Age bands used were as narrow as the available data allow. Age-specific event rates for incident MIs are taken from articles published by CVDNOR (Wisløff, 2008). An incident MI is a myocardial infarction in a person who has not previously suffered an MI. As for ischemic stroke, the Swedish data was used in patients aged 85 years or younger for event rates(Rosengren et al., 2013). For the age group over 85, the Tromsø population-based study was used since the Swedish data did not cover these event rates (Vangen-Lønne et al., 2015). The Swedish data covered a much larger number of individuals, especially for 21st-century data. Moreover, Tromsø tends to have a higher incidence of CVD compared to other municipalities in Norway. By contrast, the entire population of Sweden would be a closer match to the entire population of Norway than a single Norwegian municipality. Hence, the Swedish data was preferred when inputting data.

Individuals who survive MI or IS events are moving to post-event CVD states. Individuals in the Post-MI state are facing heightened risk for recurrent MI, IS, and all-cause mortality. Relative risks for recurrent MI and IS are taken from the NorCaD model (Wisløff,2008), and an increased risk of all-cause mortality is taken from long-term survival analysis of English national registry data(Smolina et al., 2012). Post-IS has three degrees of severity: minor, moderate, and severe. Moderate patients have the need for nursing and personal assistance for all years after IS event, while severe patients live full time in nursing homes (Wisløff, 2008 ;Wisløff et al., 2014). As mentioned above, patients with moderate or severe stroke can not go back to work. Probabilities for developing moderate or severe conditions are taken from previous analyses that utilized Swedish national stroke registry data. Patients aged over 75 are more likely to develop severe condition than younger patients (Wisløff, 2008 ;Wisløff et al., 2014). Individuals in Post-IS states are also at heightened risk of recurrent stroke, MI, and all-cause mortality(Wisløff, 2008). It is assumed that individuals cannot move from “more severe” to “less severe” health states and a stroke is presumed to be a more severe health state than MI. Hence, Post-IS patients who experience a heart attack can not move to the Post-MI state but remain in their original Post-IS state. MIs for stroke patients are captured as event costs, temporary event-based quality of life decrements, as well as the associated risk of death. Increased risks are integrated into the model as a relative risk multiplied by baseline risk. Age-specific all-cause mortality rates were obtained from the Norwegian Cause of Death registry and accessed through the Norwegian Institute of Public Health’s Statistic Bank(Statistikkbanker, n.d.). Deaths of those individuals who died of diseases other than

hypertension and CVD were also included. More details on incidence rates and relative risks are given in Appendix 1.

Baseline risks are adjusted downwards in each CVD event and all-cause death after using HealthB in addition to standard of care through the use of relative risks. This means both the CVD incidence rates and all-cause mortality goes down. The treatment cost for CVD and production loss decreases.

4.12 Model Assumptions and half-cycle correction

The model uses Norwegian population-based CVD incidence rates. The use of population-specific incidence rates, as opposed to more generalized risk equations, was chosen to reduce location bias and time bias. This decision is based on assumptions and arguments laid out in the NorCaD model and other analyses specific to cardiovascular disease in Norway. The population-specific rates in this study were taken from Norwegian registry data and publications based on registries. Generally, baseline incidence rates were from two primary sources: the Norwegian Cause of Death Registry and the Cardiovascular Disease in Norway registry (Statistikkbanker, n.d.; Sulo et al., 2014). It was assumed that incidence rates based on national registry data would be a reflection of average baseline risk. The Swedish Stroke registry was used as well, in the absence of sufficient Norwegian-specific data(Rosengren et al., 2013). It was assumed that the Norwegian and Swedish populations are quite similar. Transition probabilities were derived from population-based incidence rates. Rates were converted to probabilities within the model according to the methods mentioned above. Relative risks are multiplied by incidence rates before conversion to transition probabilities. Relative risks for hypertensive patients transition to CVD are from NorCaD, which is based its calculations on SCORE risk estimations(Wisløff, 2008). The reductions in systolic blood pressure as a result of HealthB intervention were assumed to be an average of 10 mmHg. Relative risk reductions as a result of HealthB intervention are modeled according to a meta-analysis of the effect of BP reductions on CVD risk. History of CVD results in elevated risk for further CVD events. Relative risks for those in chronic post-CVD states are taken from a variety of sources. A half-cycle correction was employed for all discounted and undiscounted cumulative outcomes including life years, QALYs, and costs.

4.13 Sensitivity Analysis

The structural uncertainty of the model was assessed through one-way deterministic sensitivity analyses. Such analyses can be used to observe the impact of key parameters on the outcome. One-way sensitivity analysis was performed on the cost of HealthB in order to identify the cost-effectiveness when the price varies from -50% to +50% of the current given price. A two-way sensitivity analysis was performed on the assumed effect of HealthB. Both relative risks for MI and IS events varied from 0.5 to 1 in order to capture cost-effectiveness conditions under different effects of HealthB. Probabilistic sensitivity analysis (PSA) was undertaken according to methods laid out by Briggs et al. (2006). This allows for the uncertainty around all parameters to be varied simultaneously in order to capture the overall uncertainty surrounding the output of the model. In this study, Dirichlet distribution is used for probabilities, Beta distribution is used for QALYs, and Gamma distribution is used for costs. Monte Carlo simulation was performed in which the model was simulated 1000 times using the random draws for each input parameter according to its respective distribution. This provides the probabilistic output of the model and a clearer picture of the uncertainty surrounding point estimates and mean output. To answer the sub-question that HealthB would be cost-effective at what price, holding a WTP of 600,000NOK/QALY and the assumption of HealthB's effect, the value of the "HealthB" parameter will be changed to find prices when HealthB has a 50% likelihood to be cost-effective across three groups of patients. Similarly, changes in effects have been done to find the minimum effect on blood pressure before HealthB is 50% possible to be cost-effective assuming a WTP of 600,000 NOK/QALY and one year price of HealthB of 10000 NOK.

5. Results

The deterministic results for three groups of patients are presented in Table 5. ICERs, incremental costs and incremental effects are shown in the table. The WTP threshold of 700,000NOK was used to calculate the ΔNMB value. Overall, the trend for QALYs, LYs, and costs was the same for both perspectives and all groups. The results from the healthcare perspective are discussed in detail below, followed by ICERs from the societal perspective.

Under the assumption that HealthB will cause an average systolic pressure reduction of 10 mmHg for each patient in the cohort, HealthB led to QALY and LY gains across three groups of population (Table 7). We can see from the table that QALY and LY gains become higher as hypertension becomes more serious, though the difference in gains is not too much between groups. Stage 3 hypertensive patients see the highest increment in QALYs, from 15807 QALYs with only common therapy, to 16069 QALYs when HealthB is added. Similarly, LY gains for stage 3 hypertensive patients are highest, increasing from19291 LYs with common practice to 19571 LYs with the addition of HealthB. QALYs for stage 2 hypertensive patients increase from 16016 to 16261 with HealthB. QALY gains for the stage 1 group are slightly smaller, from 16201 to 16420. It is worth mentioning that, with the current hypothesis, QALY and LYs gains for the stage 3 hypertension group are only slightly larger than those for the stage 1 and stage 2 groups.

The cost of treating CVD decreases with the use of HealthB for all patient groups. The biggest cost reduction is observed in Stage 3 group: 329,189,364NOK with standard treatment drops to 304,726,277 NOK with the addition of HealthB. The stage 2 group has a less CVD cost saving of around 2.6 million than the saving of the stage 3 group. Decreases in CVD costs for the stage 1 group are lowest. On the contrary, the total cost including direct medical cost and the cost for Health increases in three scenario groups. Increases in lifetime HealthB costs per patient are substantial and offset the decrease in CVD treatment costs. Stage 1 hypertensive patients see the lowest increase from 161,029,256NOK to 321,679,163NOK, while stage 2 hypertensive patients see the highest increase from 270,968,155NOK to 443,583,861NOK.

Incremental costs per QALY(ICERs) are 733,053NOK/QALY, 705,630NOK/QALY and 639,523NOK/QALY respectively for stage 1 hypertensive group, stage 2 hypertensive group and stage 3 hypertensive group. The most cost-effective patient group is the group with stage

3 hypertension, while the less cost-effective patient group is the group with stage 1 hypertension. Holding to a strict 600,000NOK WTP threshold, HealthB is not cost-effective for three groups of patients. As mentioned before, this report will consider treatments with ICERs between 600,000 and 700,000 NOK/QALY to be borderline cost-effective. Hence, the use of HealthB for grade 2 and grade 3 groups of patients is on the border of cost-effectiveness. Holding a 700,000NOK WTP threshold, the use of HealthB for grade 3 hypertensive patients will be cost-effective.

It is worth mentioning that HealthB is more cost-effective for grade 2 and grade 3 groups after considering production loss from a societal perspective. Holding a 600,000 NOK WTP threshold, HealthB is cost-effective for patients with grade 2 hypertension with an ICER of 538,682 NOK/QALY and it is more cost-effective for the grade 3 hypertension group with an ICER of 461,131 NOK/QALY. However, initiating HealthB intervention for those with stage 1 hypertension is not cost-effective with an ICER of 759,089 NOK/QALY.

Groups	**ΔQALYS**	**ΔLYS**	**ΔCOSTS(HP)**	**ICER(HP)**	**ΔCOSTS(SP)**	**ICER(SP)**
Grade 1 hypertension	291.15	266.47	160,649,906	733,053	166,355,623	759,089
Grade 2 hypertension	244.63	271.73	172,615,706	705,630	131,775,869	538,682
Grade 3 hypertension	263.15	280.95	168,289,821	639,523	121,346,064	461,131

Table 5. Deterministic Results from healthcare and societal perspective. HP represents a healthcare perspective, while SP represents a societal perspective.

Some results from sensitivity analyses are presented in Appendix 2 for the healthcare and societal perspective, respectively.

One-Way Sensitivity Analysis of Price

Since the price of HealthB will be changing, a one-way sensitivity analysis of price was performed to determine the most cost-effective strategy for each of the three patient groups, at several hypothetical price increases. From a healthcare perspective, the price varied from a 50% reduction to a 50% increase resulting in an ICER of 314,561NOK/QALY and 115,1545 NOK/QALY respectively for grade 1 hypertensive patients. The same trends can be seen when the price varied from a 50% reduction to a 50% increase for both grade 2 and grade 3 hypertension groups. When the price reaches 15000NOK, both ICERs are over 1millionNOK/QALY.

In a societal perspective with the current assumed price, HealthB was cost-effective at a WTP of 600,000 NOK/QALY for the group with stage 3 hypertension and stage 2 hypertension. With a 50% price reduction, initiation of HealthB intervention is cost-effective for the stage 1 hypertension group in addition to the other two groups. However, at a 50% price increase, HealthB is not cost-effective across for any patient groups. So, if the price of HealthB is 15000NOK, ICERs for the grade 1 hypertension group will be over 1 million NOK/QALY, while the ICER for grade 2 and 3 hypertension groups will come close to 1 million NOK/QALY. If the price increases more than 50%, ICERs will be higher.

Two-Way Sensitivity Analysis of the effect of HealthB on MI and IS Incidence

This study makes the main assumption that HealthB has an effect on MI and IS and uses this 0,83 and 0,73 relative risk estimate, despite the fact that data is not based on the random clinical trial of HealthB. Hence, a two-way sensitivity analysis was undertaken to determine the effect of this assumption on the result in an effort to explore structural uncertainty. Overall, the trend of the results was the same for both perspectives and three groups. Only the results from the healthcare perspective are discussed. As mentioned, all tables can be found in Appendix 2.

From Appendix 2, it can be observed that the relative risk for both MI and IS events after using HealthB varied from 0.5 to 1. Across three groups, the highest ICER was observed when both relative risks were set at 1, which means HealthB has no effect in reducing risks of MI and IS events. However, the lowest ICER was observed when both relative risks were set at 0.5. For grade 1 hypertensive patients, HealthB is borderline cost-effective when both relative risks are 0.7 holding a WTP threshold of 600,000NOK/QALY. With the same threshold value, relative risks for grade 2 group should be 0.8 for MI and 0.6 for IS respectively in order for HealthB to be borderline cost-effective. For grade 3 group, the relative risk of IS could be 0.7 while keeping the 0.8 for MI unchanged as grade 2 group.

Probabilistic Sensitivity Analysis

From the healthcare perspective, in the cost-effectiveness plane of the grade 1 hypertension group (Figure 2), we can see that all the simulated ICERs from the PSA are in the northeast and northwest quadrant. This implies that the new intervention was more costly and might generate fewer LYs and QALYs in comparison with the current standard of care.

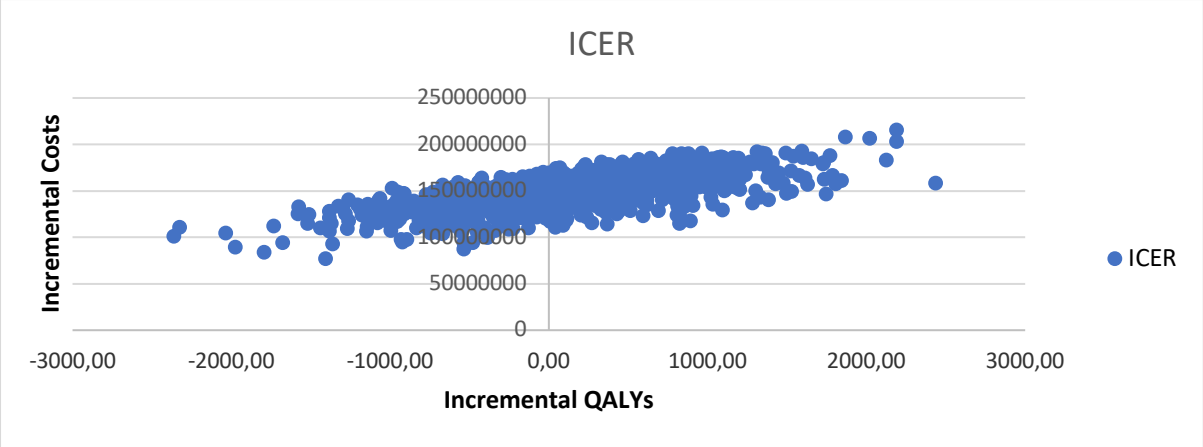

Figure 2. Scatterplot of Simulated ICERs in societal perspective : grade 1 hypertensive patients

However, approximately 90% of all the simulated ICERs for both grade 2 and grade 3 groups in the healthcare perspective resulted in the northeast quadrant in the cost-effectiveness plane. This implies that most simulations had higher costs and more QALY gained.

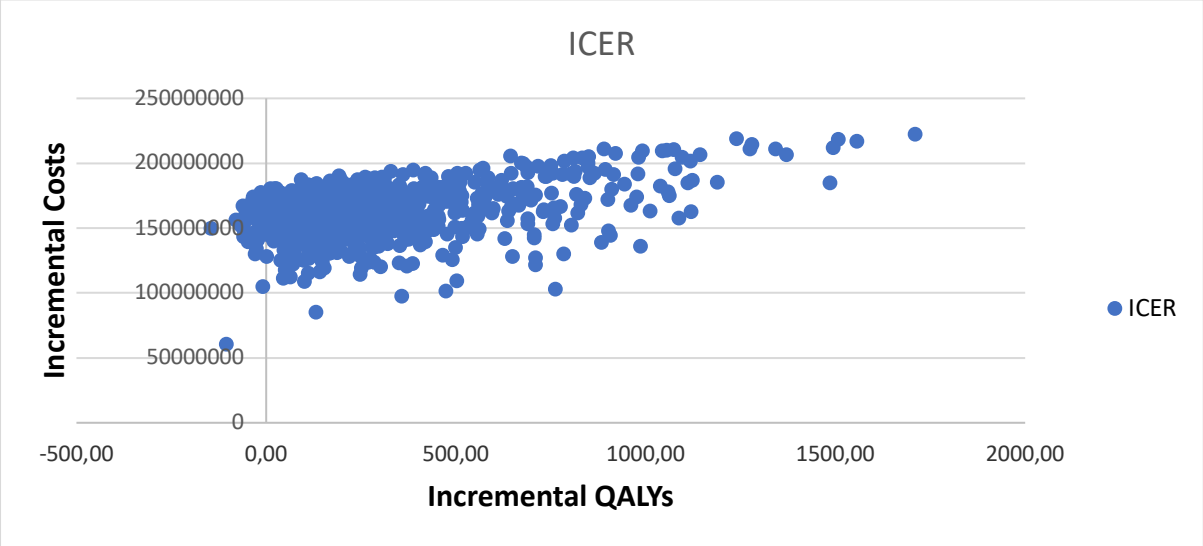

Figure 3. Scatterplot of Simulated ICERs in societal perspective (HP): grade 2 hypertensive patients

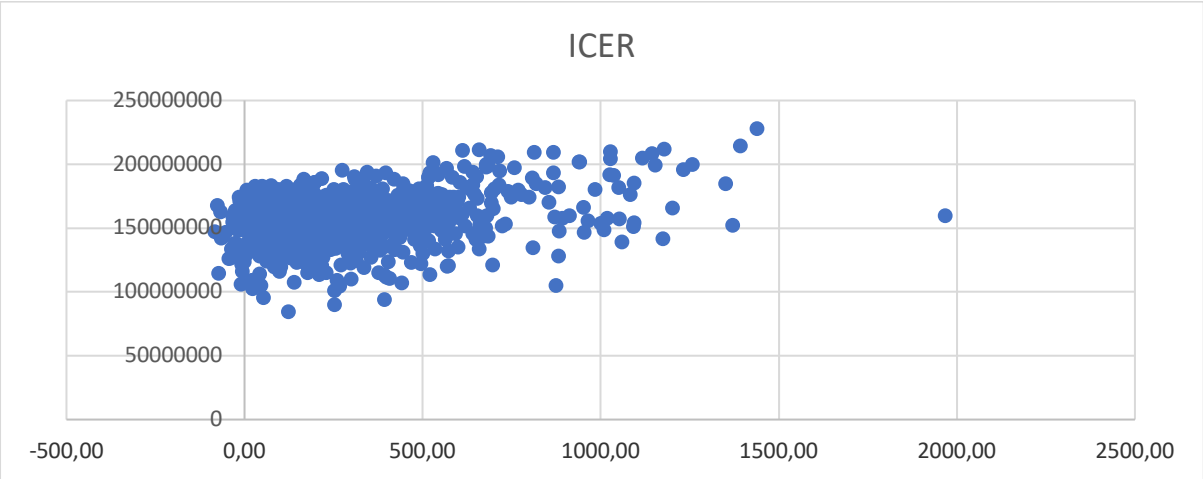

Figure 4. Scatterplot of Simulated ICERs in societal perspective: grade 3 hypertensive patients

Cost-Effectiveness Acceptability Curves

Cost-effectiveness acceptability curves (CEACs) from probabilistic sensitivity analysis indicate that there is a probability that HealthB is cost-effective given a 600,000-700,000 NOK/QALY threshold for patients with three grades of hypertension. From a healthcare perspective, at a WTP threshold of 600,000 NOK/QALY, the probability that HealthB is cost effective for grade 2 hypertensive patients is 32% (Figure 6). The grade 3 hypertension group has a higher probability with 37% (Figure 7). With a 700,000 NOK/QALY WTP threshold, the probability that HealthB is cost-effective is 37% for grade 2 hypertensive patients and 42% for grade 3 hypertensive patients. For the group of the grade 1 hypertensive patients, both probabilities are 36% (Figure 5). It is worth noting that the incremental net monetary benefit is negative for this group of patients. It means the initiation of HealthB is not cost-effective compared to common practice.

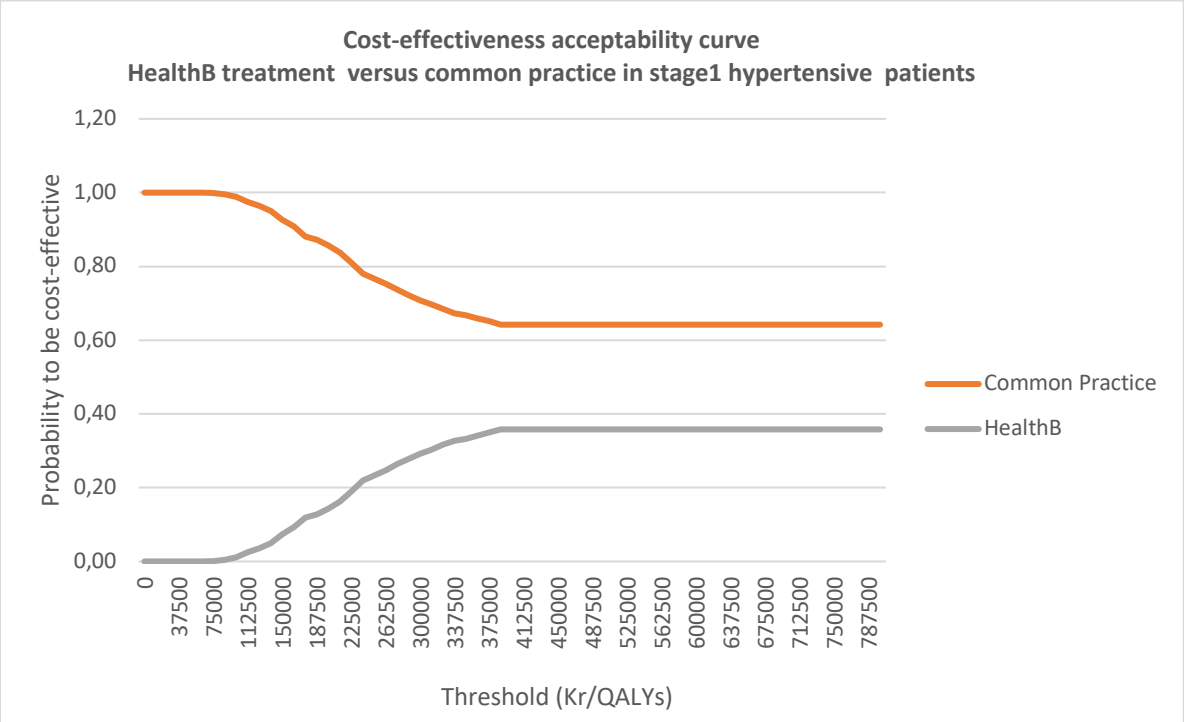

Figure 5

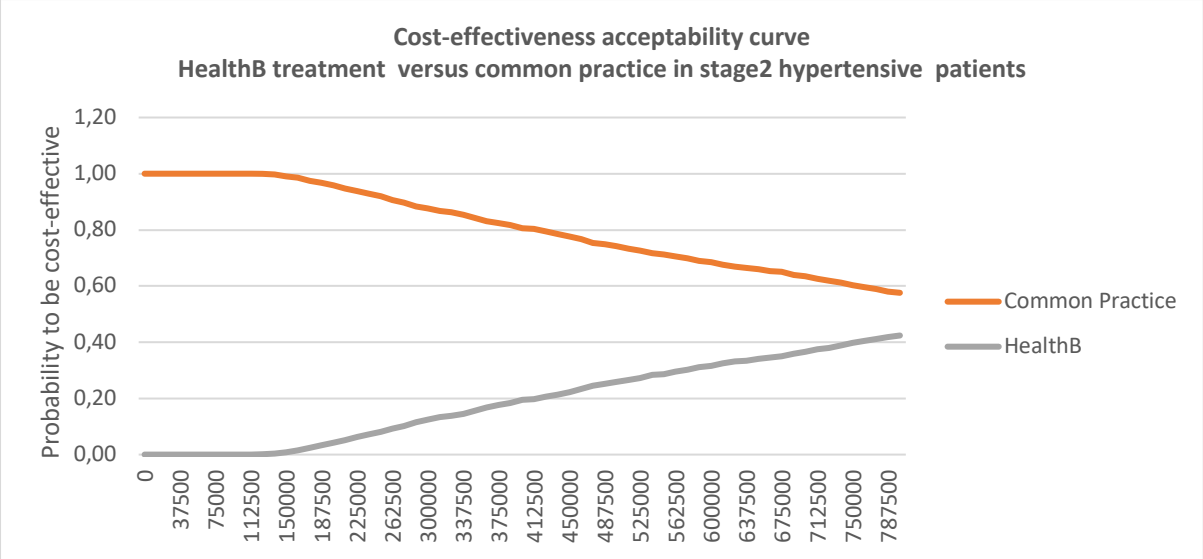

Figure 6

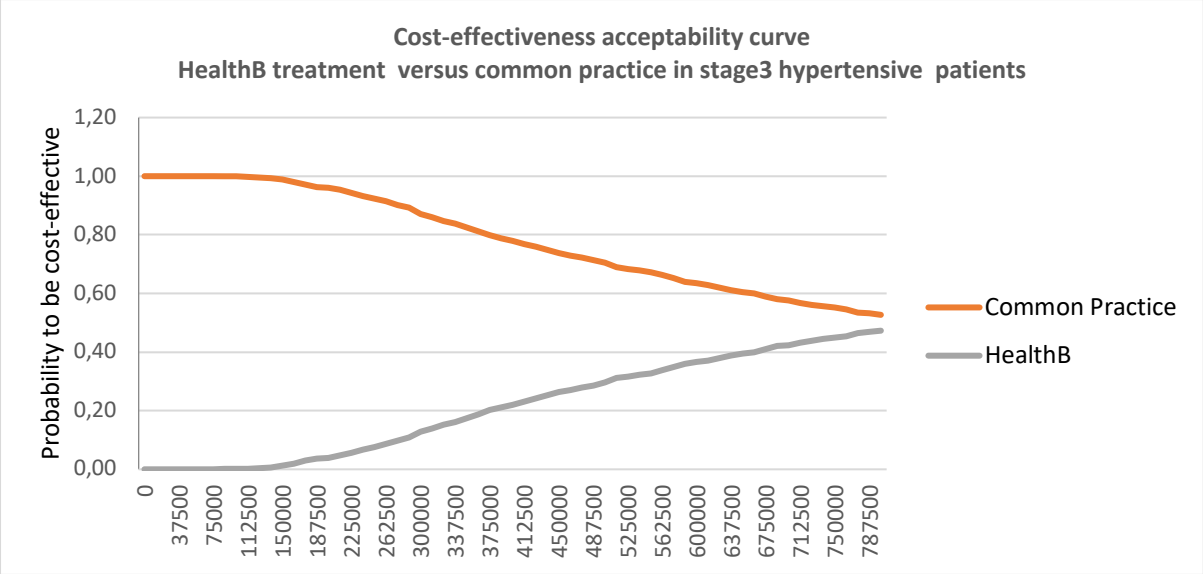

Figure 7

To answer two sub-questions more comprehensively, more probability sensitivity analyses have been performed to find the minimum effect on blood pressure and the maximum price of HealthB before HealthB is 50% possible to be cost-effective across three groups of patients. We can see from Figure (8-10), the price should be 7395NOK, 6500NOK and 8000NOK respectively for grade 1, 2 and 3 hypertension groups when the probability that HealthB is cost-effective is 50% assuming a WTP of 600,000NOK/QALY and the same effect on blood pressure mentioned previously. These three prices are lower than our assumed price in the model.

Assuming a WTP of 600,000NOK/QALY and a price of HealthB of 10000NOK for one year (base price), the relative risks of MI and IS after using HealthB should be 0.66 and 0.58, 0.66 and 0.55 as well as 0.71 and 0.65 respectively for grade 1, 2 and 3 hypertension groups when HealthB is 50% possible to be cost-effective. Compared to the base effect, they are lower across three groups. This demonstrates that HealthB should have a greater effect on blood pressure control than the assumption if three groups want to see a higher possibility of cost-effetiveness.

6. Discussion

6.1 Main findings

To our knowledge, there are few early CEAs of digital healthcare platforms globally. This study is the first early CEA to assess the potential cost-effectiveness of HealthB in the prevention of cardiovascular diseases through its effect on hypertension in Norway and the first study on any cost-effectiveness aspect of HealthB. The study has the potential to show how HealthB can reduce the risk of CVD, and may provide a reference to further study on HealthB.

The performed study resulted in a higher cost from both a healthcare and societal perspective but yielded higher QALYs and life years. This led to fewer hypertensive patients progressing to more severe comorbidities(MI and IS in this study), thus incurring a lower cost in CVD treatment and less production loss. These costs are found to be a large cost driver in the more severe health states. In this study, with a WTP threshold held to be 600,000NOK/QALY, cost-effectiveness was not found in three different grades of hypertension groups from a healthcare perspective, though grade 1 and grade 2 hypertension groups can see cost-effectiveness from a societal perspective. A one-way and a two-way sensitivity analysis were performed in the study. It was found that the price for HealthB could be higher if the relative risk reduction would increase further as the ICER would still be under the WTP threshold value with a lower cost of CVD treatment.

From the "background" part, it was explained how HealthB works in the management of hypertension and prevention of CVDs. However, HealthB is not an alternative to common treatment for hypertension but an addition to common practice. Due to the prevalent nonadherence among hypertensive patients, HealthB could improve patients' health literacy and provider engagement and play a part in their adherence to antihypertensive medications and consequently in blood pressure management. Since HealthB is under development and there is no experimental data, an estimated systolic pressure reduction of 10 mmHg was used to evaluate the deterministic result of using HealthB in addition to antihypertensive drugs.

6.2 Previous Study

The domain of healthcare has been moving into the digital world recently. Digital health solutions are conceived and delivered by healthcare providers through the use of information

and communication technologies to monitor and improve the well-being of patients and to empower patients in the management of their health (Iyawa et al., 2016).

Despite this research being the first CEA of HealthB, several CEAs of other digital health solutions have been performed. Darden et al. (2021) examined the cost-effectiveness of a digital cognitive behavioral therapy (CBT) intervention for insomnia. They found that compared to other insomnia treatments, digital CBT was the most cost-effective treatment because it had the smallest ICER. Bhardwaj et al. (2021) assessed the cost-effectiveness of a digital health intervention (DHI) in reducing 30-day readmissions among AMI patients. The results demonstrated that this DHI is cost-saving through the reduction of hospital readmissions and associated costs.

Although there are several studies showing that digital solutions are cost-effective, it is hard to make a general conclusion about the cost-effectiveness of these digital solutions because estimating program costs and outcomes are difficult. The main challenges included limited or lack of cost data, inappropriate cost measures, difficulty with identifying and quantifying effectiveness, etc. Although the conclusion about the cost-effectiveness is pending, digital platforms can help optimize diagnosis, consulting, and treatment of patients in general(Senbekov et al., 2020).

6.3 Strengths and Limitation

This study incorporates the first decision-analytic model for the potential outcomes of HealthB. The structure of the model and the states have been used in other papers, though the model used in this thesis has been simplified compared with the model used in other studies(Wisløff, 2014; Enden et al., 2013). The fact that both MI incidence rates and all-cause mortality rates come from Norwegian registry data is a major strength of this analysis. This data is consistent and reliable, with minimal manipulation to synthesize it together. Deterministic sensitivity analyses performed in this thesis provide insight into how the parameters “cost of HealthB “and “relative difference in risks after using HealthB” impact the cost-effectiveness of HealthB. The PSA performed allowed conclusions to be drawn regarding the likelihood of HealthB being cost-effective despite the uncertainty inherent in the parameter data.

Another strength of the model was the age-specific rates. Three groups of patients were tested at different ages and the age band was as narrow as possible. This allowed for differentiated and precise results which are important when the decision maker has specific needs for a certain age group. The costs used in this report are also a considerable strength. The cost data provide a comprehensive description of CVD costs in Norway. As stated previously, costs from the NorCaD model are frequently used in Norwegian economic evaluations.

The lack of data on the actual effect of HealthB on hypertension and CVD and the subsequent need to make assumptions was a major limitation. Although an early cost-effectiveness analysis was performed based on an assumption of effect, the results produced by this analysis can still indicate a degree of predictive validity since a two-way sensitivity analysis and PSA have been developed to see the cost-effectiveness of different relative risk reductions caused by HealthB. This model only considers the positive effect of HealthB on blood pressure and CVD. However, HealthB may also cause negative effects due to incorrect operation or other factors. It would be interesting for future research to study whether similar health information technology interventions will have adverse impact under improper operation.

IS rates from Swedish registry data are one of the limitations. There could be some inconsistencies with other incidence rates from Norwegian contexts. As the populations of these two countries are quite matched, this limitation is not possible to cause a big difference. To simplify the analysis, the gender-combined rates were used in the model. It is a potential limitation, as discussions might be more comprehensive if differences in female and male populations are considered.

There are some limitations with the utility values in the model. Post-MI and Post IS are very broad categories. There is a large amount of variation observed between patients after MI and IS events, but this model did not differentiate according to chronic CVD complications. This makes utility values of Post MI and Post IS a little bit problematic. When there is further research about HealthB, these states are better to be divided into smaller entities.

The model does not include angina and heart failure as CVD states. The epidemiology of these two diseases can be difficult to determine and there is limited data on them. It is possible that to some extent the model might underestimate health gains and cost savings associated with possible reductions in angina and heart failure.

The literature search for this report was conducted in some ways strong and in others quite limited. The consolidation of Norwegian registry data simplified the search for incidence rates and probability parameters. NorCaD provides strong cost data and an overview of previous CVD economic evaluation models(Enden et al., 2013). However, there is no previous cost-effectiveness analysis of HealthB due to its novelty. Moreover, the huge scope of CVD means a comprehensive literature review, which was infeasible given the time and resources available. In summary, more research needs to be conducted as clinical data become available to assess the predictive validity of this study and to assess the factual value of HealthB.

7 Conclusion

HealthB is not cost-effective from a healthcare perspective with a WTP of 600,000NOK/QALY. This applies to all patient groups tested. From a societal perspective, HealthB is cost-effective for patients with grade 2 and 3 hypertension because these two groups can see a bigger societal cost-saving than group 1. This conclusion is drawn under assumptions of effect and cost of HealthB. There is also more to do with the structure of the model. Future research is needed to determine the factual effect of HealthB on blood pressure reduction. Trials should include as many cardiovascular disease-related clinical endpoints as possible. Future cost-effectiveness analyses should split CVD states into as many separate entities as is feasible in order to resolve uncertainty when modeling health-related quality of life.

Appendix1

Methods summary

A Markov model was used to estimate the effect of HealthB on the lifetime risk of myocardial infarction and ischemic stroke. Each cycle length is one year and all individuals are at risk of experiencing MI, IS, and all-cause death. Patients begin in the hypertension state and remain there until they experience a cardiac event or die. Individuals who survive cardiac events are moving to the post-MI or post-IS.

Norwegian population-based incidence and event rates were mostly used because they reduce bias due to time and geography. Swedish registry data or other studies were used when Norwegian data was unavailable. Relative differences in risk in post-CVD states were taken from a wider variety of studies and meta-analyses from Scandinavia and Europe because there is not enough data solely on Norwegian studies. Relative risks are used to adjust baseline incidence rates up or down as necessary.

Each cardiac event and post-CVD health state has a number of cost components. All relevant CVD costs are in the Norwegian healthcare system. Utility values associated with each state or event are taken from cohort studies or other analyses. Both LYs and QALYs are estimated for each cycle. The model is primarily measured through the ICER.

Here are the values of parameters used in the model. They are classified in different tables and all of them correspond to the contents in the “Methods” part.

Table 6. Population Incidence Rates for Myocardial Infarctions

Age	Incidence rates	Source
25-44	0.00031358	(Sulo et al., 2014)
45-64	0.00286695	(Sulo et al., 2014)
65-84	0.01108764	(Sulo et al., 2014)
85+	0.03315512	(Sulo et al., 2014)

Table 6. Age-specific population incidence rates for first-ever myocardial infarction in Norway

Table 7. Population Incidence Rates for Ischemic Strokes		
Age	Incidence Rates	Source
18-44	0.00009109	(Rosengren et al., 2013)
45-54	0.00058083	(Rosengren et al., 2013)
55-64	0.00173558	(Rosengren et al., 2013)
65-74	0.00433296	(Rosengren et al., 2013)
75-84	0.00909593	(Rosengren et al., 2013)
85+	0.01841689	(Vangen-Lønne et al., 2015)

Table 7. Age- specific population incidence rates of first-ever strokes in Sweden

Table 8. Population All-Cause Mortality Rates		
Age	**Incidence Rates**	**Source**
40-44	0.00091803	(Statistikkbanker, n.d.)
45-49	0.00156034	(Statistikkbanker, n.d.)
50-54	0.00275075	(Statistikkbanker, n.d.)
55-59	0.00415172	(Statistikkbanker, n.d.)
60-64	0.00675465	(Statistikkbanker, n.d.)
65-69	0.01123460	(Statistikkbanker, n.d.)
70-74	0.01836237	(Statistikkbanker, n.d.)
75-79	0.03216226	(Statistikkbanker, n.d.)
80-84	0.05865050	(Statistikkbanker, n.d.)
85-89	0.10642763	(Statistikkbanker, n.d.)
90-94	0.19958414	(Statistikkbanker, n.d.)
95+	0.33822281	(Statistikkbanker, n.d.)

Table 8. Age-specific all-cause mortality rates in Norway.

Table 9. Relative Risk of Hypertension					
Systolic Blood pressure by age (per 20 mmHg)	**RR MI**	**(SE)**	**RR IS**	**(SE)**	**Source**
40-49	1.58	(0.101)	1.76	(0.123)	(Wisløff, 2008)
50-59	1.43	(0.11)	1.55	(0.147)	(Wisløff, 2008)
60-69	1.31	(0.116)	1.35	(0.124)	(Wisløff, 2008)
70-79	1.2	(0.096)	1.24	(0.119)	(Wisløff, 2008)
80+	1.06	(0.047)	1.07	(0.061)	(Wisløff, 2008)

Table 9. Age-specific relative risks of hypertension.

Table 10. Post MI Relative Risks and Probabilities			
	Value	**(SE)**	**Source**
RR MI Recurrence	3.05	(0.291)	(Wisløff, 2008)
RR Post-MI to Stroke	2.77	(0.131)	(Wisløff, 2008)
RR Post-MI to All-Cause Mortality			
30-54	1.9	(0.068)	(Smolina et al., 2012)
55-64	2.66	(0.048)	(Smolina et al., 2012)
65-74	2.161	(0.059)	(Smolina et al., 2012)
75-84	1.781	(0.072)	(Smolina et al., 2012)
85-89	1.260	(0.103)	(Smolina et al., 2012)
90+	1		

Table 10. Increased risk of CVD and all-cause mortality for Post-MI patients. The RR value for those aged 90 and above was assumed to be 1.

Table 11. Post-IS Relative Risks			
	Value	**(SE)**	**Source**
Prob. Moderate (<75 years)	0.3		(Wisløff, 2008;Wisløff et al., 2014)
Prob. Severe (<75 years)	0.105		(Wisløff, 2008;Wisløff et al., 2014)
Prob. Moderate Sequelae (>75 years)	0.48		(Wisløff, 2008;Wisløff et al., 2014)
Prob. Severe Sequelae (>75 years)	0.2		(Wisløff, 2008;Wisløff et al., 2014)
RR Post-IS to MI	3.51	(0.28)	(Wisløff, 2008)
RR Stroke Recurrence	2.82	(0.167)	(Wisløff, 2008)
RR Post-IS All-Cause Mortality (40-79 years)	3.4	(0.113)	(Mathisen et al., 2016;Rutten-Jacobs et al., 2013)
RR Post-IS All-Cause Mortality (80+ years)	1		(Mathisen et al., 2016;Rutten-Jacobs et al., 2013)

Table 11. Probability of different severity degree of Post-IS, risk of CVD, and risk of all-cause mortality after incident ischemic stroke.

Table 12. All direct medical costs used in the model					
Cost Parameter	Number of Services	Cost Component		Unit Cost (NOK)	Total Cost (NOK)
Cost of Stroke (first year)					
	1	One year treatment for stroke			248,612
Source: (Wisløff, 2008;Wisløff et al., 2014)					
		Total			**248,612**
Cost of Minor Post-IS (after one year year)					
	2	GP visit			
	2	GP lab test			865
Source: (Wisløff, 2008; Normaltariff, n.d.)					
	1	Aspirin			421
	1	Beta Blocker			945
	1	Statin			1324
	1	ACE-inhibitor			452
Source:(Legemiddelverk, n.d.; Legemiddelforbruket, n.d.)					
		Total			**4,007**
Cost of Moderate Post-IS					
	1	Total Care Costs			78,767
Source: (Wisløff, 2008;Wisløff et al., 2014)					
Cost of Severe Post-IS					
	1	Total Care Costs			1,127,262
Source: (Wisløff, 2008;Wisløff et al., 2014)					
Cost of MI					
	0.4	Hospital with PCI facilities		100,680	40,272
	0.6	Hospital without PCI facilities		278,929	167,358
Source: (Wisløff, 2008)					
		Total			**207,630**
Cost of Hospital with PCI Facilities			**DRG weight**		
	1	Ambulance		14,299	14,299
Source: (Wisløff, 2008;Wisløff et al., 2014)					
	1	GP visit		320	320
Source: (Wisløff, 2008; Normaltariff, n.d.)					
	0.5	DRG 112E	1.71	80,594	40,296
	0.5	DRG 112F	1.942	91,527	45,764
Source: (Wisløff, 2008; Innsatsstyrt finansiering, n.d.)					
		Total			**100680**
Cost of Hospital without PCI Facilities					
	2.8	Ambulance		14,299	40,037
Source: (Wisløff, 2008;Wisløff et al., 2014)					
	1	GP visit		320	320
Source: (Wisløff, 2008; Normaltariff, n.d.)					
	1.4	DRG 122	0.7	32,992	46,187
	0.5	DRG 121	1.218	57,405	28,702
Source: (Wisløff, 2008; Innsatsstyrt finansiering, n.d.)					
	2.8	Ambulance		14,299	40,037
	0.45	DRG 112E	1.71	80,594	36,267
	0.45	DRG 112F	1.942	91,527	41,187

1.4	DRG 122	0.7	32,992	46,188
	Total			**278,929**
Cost of Post-MI				
2	GP visit			
2	GP lab test			865
Source: (Wisløff, 2008; Normaltariff, n.d.)				
1	Aspirin			421
1	Beta Blocker			945
1	Statin			1324
1	ACE-inhibitor			452
Source:(Legemiddelverk, n.d.; Legemiddelforbruket, n.d.)				
	Total			**4,007**

Table 12. Direct costs used in the model pertaining to treating and preventing CVD. All costs are 2022 Norwegian Kroner (NOK)

Appendix 2

One-way sensitivity analysis

cost HealthB	Incr. cost	Incr. QALY	ICER
5000	66898305,3	219,15	305260,236
10000	166355623	219,151718	759088,838
15000	265812941	219,151718	1212917,44

Table13. Grade 1 hypertension from a societal perspective

cost HealthB	Incr. cost	Incr. QALY	ICER
5000	68936590,7	219,15	314561,032
10000	160649906	219,151718	733053,373
15000	252363222	219,151718	1151545,71

Table14. Grade 1 hypertension from a healthcare perspective

cost HealthB	Incr. cost	Incr. QALY	ICER
5000	73912986,5	244,63	302146,597
10000	172615706	244,626242	705630,372
15000	271318426	244,626242	1109114,15

Table15. Grade 2 hypertension from a healthcare perspective

cost HealthB	Incr. cost	Incr. QALY	ICER
5000	33073149,4	244,63	135198,698
10000	131775869	244,626242	538682,473
15000	230478588	244,626242	942166,248

Table16. Grade 2 hypertension from a societal perspective

cost HealthB	Incr. cost	Incr. QALY	ICER
5000	23016812,8	263,15	87466,8589
10000	121346064	263,148958	461130,704
15000	219675316	263,148958	834794,55

Table17. Grade 3 hypertension from a societal perspective

cost HealthB	Incr. cost	Incr. QALY	ICER
5000	69960569,3	263,15	265859,192
10000	168289821	263,148958	639523,037
15000	266619072	263,148958	1013186,88

Table18. Grade 3 hypertension from a healthcare perspective

Two-way sensitivity analysis

		rrMI					
759,089		0,5	0,6	0,7	0,8	0,9	1
rrST	0,5	391848,632	446769,331	512581,52	592925,429	693263,386	822183,209
	0,6	432162,258	492330,979	564833,357	653939,392	766143,654	911831,182
	0,7	474612,798	540555,095	620481,485	719413,485	845099,936	1010159,83
	0,8	519381,658	591689,8	679876,978	789865,616	930937,503	1118509,6
	0,9	566671,086	646014,7	743420,634	865896,649	1024609,93	1238511,13
	1	616707,27	703846,065	811572,124	948207,71	1127254,88	1372168,34

Table19. rrMI vs rrST from a societal perspective in grade 1 hypertensive patients

		rrMI					
733,053		0,5	0,6	0,7	0,8	0,9	1
rrST	0,5	385622,882	437864,773	500422,882	576745,804	672008,292	794346,029
	0,6	419734,364	476518,39	544896,757	628884,194	734586,99	871769,298
	0,7	455599,203	517371,704	592197,063	684763,135	802303,862	956599,701
	0,8	493366,842	560630,336	642616,633	744817,697	875840,664	1049981,89
	0,9	533203,886	606525,994	696489,77	809552,62	956004,693	1153308,3
	1	575296,65	655320,756	754199,865	879556,86	1043759,09	1268290,13

Table20. rrMI vs rrST from a healthcare perspective in grade 1 hypertensive patients

		rrMI					
538,682		0,5	0,6	0,7	0,8	0,9	1
rrST	0,5	262424,547	306215,832	359635,912	426304,932	511912,906	625946,219
	0,6	300091,34	348935,235	408897,031	484313,118	582106,934	714056,884
	0,7	339790,579	394218,289	461481,718	546782,113	658564,463	811513,742
	0,8	381697,41	442309,6	517745,554	614255,608	742173,08	919899,533
	0,9	426007,334	493485,484	578096,219	687368,768	833995,594	1041174,66
	1	472939,263	548059,304	643003,407	766868,339	935315,543	1177797,03

Table21. rrMI vs rrST from a societal perspective in grade 2 hypertensive patients

		rrMI					
705,63		0,5	0,6	0,7	0,8	0,9	1
rrST	0,5	356812,209	408270,519	471016,591	549293,542	649770,631	783566,929
	0,6	390209,93	446450,208	515461,236	602223,511	714688,923	866385,596
	0,7	425346,02	486851,809	562828,25	659138,705	785303,264	957876,462
	0,8	462370,882	529687,936	613430,932	720525,52	862421,535	1059508,88
	0,9	501452,385	575198,758	667628,471	786952,175	947011,094	1173102,83
	1	542778,49	623656,632	725834,686	859086,701	1040240,2	1300940,1

Table22. rrMI vs rrST from a healthcare perspective in grade 2 hypertensive patients

		rrMI					
461,131		0,5	0,6	0,7	0,8	0,9	1
rrST	0,5	189858,03	228892,233	278203,431	342527,491	430030,554	556102,427
	0,6	228440,522	273345,772	330550,678	405973,276	510045,471	663031,523
	0,7	269381,249	320866,077	387037,161	475287,522	598964,442	784876,098
	0,8	312904,995	371783,058	448174,385	551322,775	698357,393	924981,318
	0,9	359265,634	426475,212	514561,143	635104,329	810185,26	1087771,8
	1	408751,007	485378,925	586902,99	727876,355	936929,87	1279225,31

Table23. rrMI vs rrST from a societal perspective in grade 3 hypertensive patients

		rrMI					
639,523		0,5	0,6	0,7	0,8	0,9	1
rrST	0,5	287921,354	336472,771	397764,038	477664,883	586296,763	742734,637
	0,6	321033,714	375021,361	443747,229	534302,017	659184,859	842675,837
	0,7	356081,408	416130,985	493255,289	596049,378	740030,807	956366,911
	0,8	393249,764	460078,052	546724,764	663650,405	830238,858	1086892,93
	0,9	432748,079	507179,662	604666,686	737999,163	931563,002	1238334,48
	1	474813,64	557801,401	667683,185	820180,563	1046223,13	1416204,5

Table24. rrMI vs rrST from a healthcare perspective in grade 3 hypertensive patients

Appendix 3

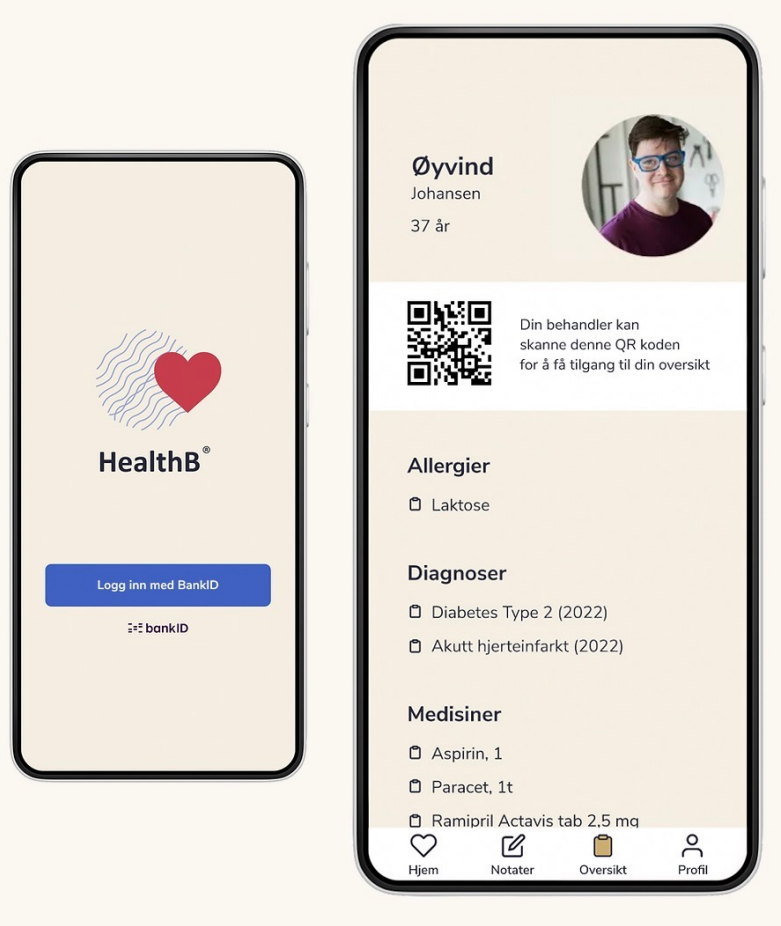

Figure8. Current interface of HealthB

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