Glucose-lowering drugs for patients with type 2 diabetes mellitus

A cost-utility analysis in a Norwegian setting

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CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CEAF	Cost-effectiveness acceptability frontier
CHD	Coronary heart disease
CUA	Cost-utility analysis
CVD	Cardiovascular disease
DRG	Diagnosis-related group
DSA	Deterministic sensitivity analysis
EQ-5D	European Quality of Life 5 dimensions
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
LY	Life year
NMB	Net monetary benefit
NoMA	Norwegian Medicine Agency
oGLD	Other Glucose-lowering drugs
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
SGLT2	Sodium-glucose co-transporter 2
WTP	Willingness-to-pay

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Abstract

Background

In Norway, about 250,000 individuals are diagnosed with diabetes, and about 200,000 of them are diagnosed with type 2 diabetes mellitus. The most common serious diabetes-related events are cardiovascular diseases, such as myocardial infarction and stroke. There are different types of glucose-lowering drugs to help prevent these events, but the drugs have negative side effects.

Research objective

The thesis is designed to compare the cost-effectiveness of sodium-glucose co-transporter 2 (SGLT2) inhibitors with other glucose-lowering drugs.

Methods

A Markov model is developed with 4 initial events and 8 health states. There are costs and health effects associated with all the health states. Costs are considered from a health care perspective, and the health effects are measured in quality-adjusted life-years (QALYs) and life years (LY) gained. A lifelong time horizon is chosen. Both deterministic and probabilistic sensitivity analysis was performed.

Results

The incremental cost of SGLT2 inhibitors compared to other glucose-lowering drugs is NOK 49,617. The incremental effect of SGLT2 inhibitors is 0.30 QALYs and 0.42 LYs gained, giving the incremental cost-effectiveness ratios of NOK 166,000 per QALY and NOK 117,000 per LY. Assuming a threshold of NOK 475,000 per QALY, simulations indicate a 68.3% probability that SGLT2 inhibitors are cost-effective.

Conclusion

SGLT2 inhibitors are cost-effective compared to other glucose-lowering drugs for WTP threshold values of NOK 475,000.

1 Introduction

1.1 Introduction

In Norway, about 200,000 are diagnosed with type 2 diabetes mellitus (T2DM) (Diabetesforbundet, 2016b), which represents about 4% of the Norwegian population. In addition, there are many people having T2DM without a diagnose, so the total number of patients in Norway with T2DM is therefore likely to be between 300,000 and 400,000 (Diabetesforbundet, 2016b).

Due to so many people having T2DM and the increased focus on diet and overweight, the topic is of high relevance. For the patients living with T2DM, it is important to get the best treatment available, and antidiabetic drugs is often used. There are a lot of medications within T2DM, and a new drug within the sodium-glucose co-transporter 2 (SGLT2) inhibitors group, Invokana, was launched in Norway this spring (Felleskatalogen, 2019c).

Cost-effectiveness analysis has previously been conducted within T2DM in the Nordic countries and in Norway. Most of the analysis look into one drug compared to another drug, and often as add-on to Metformin. I have not been able to find any cost-utility analysis looking into the SGLT2 inhibitors-group in Norway.

1.2 Research question

The objective of this cost-utility analysis is to compare the cost-effectiveness of SGLT2 inhibitors with other glucose-lowering drugs (oGLD) in Norway.

1.3 Structure of the thesis

The paper is organized into 7 sections: Introduction, Background, Theoretical framework, Methods, Results, Discussion and Conclusion. Section 2 presents background information on T2DM, its symptoms, risk-factors, its disease-related complications and treatment. Section 3 reviews theory in economic evaluation. Section 4 outlines the methodology utilized for this cost-utility analysis and methods that address the uncertainty in parameters such as probabilistic sensitivity analysis (PSA). Section 4 also describes the model inputs. Section 5

outlines the findings from analysis on the incremental cost-effectiveness ratio and presents the findings for quality adjusted life years (QALYs) and for life years (LYs) gained. Section 6 is devoted to discussion and limitations of this analysis. Section 7 concludes this cost-utility analysis.

2 Background

2.1 Type 2 diabetes mellitus

Diabetes is a chronic metabolic disease caused by insulin deficiency, insulin resistance or a combination of these factors. Insulin is a hormone that regulates the movement of sugar into the cells. There are many types of diabetes, and T2DM is the most common one. In T2DM, the body either resists the effects of insulin, or does not produce enough insulin to maintain normal glucose levels (Norsk Helseinformatikk & Norsk Elektronisk Legemiddelhåndbok, 2018a).

According to The Norwegian electronic doctor´s manual (Norsk Helseinformatikk & Norsk Elektronisk Legemiddelhåndbok, 2018a), 10-15% of people above 60 years had T2DM in Norway in 2014. In addition, the prevalence has tripled in the last 30 years, probably due to the population getting older, less physically active and more overweight. According to the Norwegian Diabetes Association (Diabetesforbundet, 2016a), investigations have shown that for each 100th patient with known diabetes, there are between 50 and 100 patients with undiscovered diabetes. Including the undiscovered cases, the total number of patients in Norway with T2DM can therefore be approximately 300,000 to 400,000.

Due to the fact that a significant proportion of those with T2DM have not been diagnosed, there will exist uncertainty for several parameters of the disease burden. The total number of people with diabetes can only be calculated by extrapolating from smaller studies (Folkehelseinstituttet, 2016). Those who are discovered during such investigations will receive medical follow-up, while those who have the disease without knowing will not have any follow-up. This makes it impossible to know the true numbers of mortality and morbidity of undiagnosed patients throughout the population. Mortality and health loss can also be differently distributed among diagnosed and undiagnosed people (Folkehelseinstituttet, 2016).

T2DM can affect all ages, although the disease is more common to occur after the age of 40. Genetics, overweight and obesity, diet and lack of physical activity are the most important factors that can cause or increase the chances of developing T2DM (Diabetesforbundet, 2016b). According to the DECODE study group, which looked at 13 studies from nine European countries, there are still problems related to the detection, diagnosis, management, and prevention of diabetes (The DECODE Study Group, 2003).

Despite the uncertainty associated with the proportion of the population with diabetes, estimates from Global Burden of Diseases (GBD) show that diabetes is an important cause of both mortality and health loss in Norway (Folkehelseinstituttet, 2016). According to the report, diabetes is in the 13th place when it comes to the main causes of death, 15th place among causes of life years lost, and in 7th place among causes of loss in the individuals well-being.

2.2 Symptoms

The symptoms of untreated T2DM are most often diffuse and develop over time. Due to high blood sugar, the most common symptoms are increased thirst, increased urination, feeling tired and unexplained weight loss. In addition, some people may experience blurred vision, fatigue, increased hunger and episodes with increased infections (Mayo Clinic, 2019). Some people go for years without the disease being detected due to diffuse symptoms, and for some, the disease is first discovered at the hospital with admission for other serious conditions.

2.3 Risk factors

Not all populations or people are presented with the same risk for T2DM. For example, minority populations and populations in developing countries are at high risk of developing T2DM (Fletcher, Gulanick, & Lamendola, 2002). Ethnicity, genetics and lifestyle play an important role in determining a person´s risk factors for T2DM. Risk factors are defined as those aspects of an individual's lifestyle, environment, or genetic traits that are known through epidemiologic study to be associated with occurrence of disease.

It is still not known why some people develop T2DM, and some do not, but it is clear that certain factors increase the risk. This includes strong family history of diabetes, people of older age, obesity, and physical inactivity. In addition, people having the associated metabolic abnormalities such as hypertension, elevated triglycerides and low high-density lipoprotein (HDL) cholesterol, are at higher risk. The greater the number of risk factors an individual has, the greater the chance of developing T2DM and its associated complications (Fletcher et al., 2002).

2.4 Diabetes-related complications

Patients with T2DM are at risk of developing other diabetes-related complications, due to uncontrollable diabetes. The most common acute complications include hypo- and hyperglycemia (low and high blood sugar) and diabetic coma. The most common serious complications are coronary artery disease, stroke, kidney failure, blindness and foot disease. Early detection and treatment of T2DM enhances prevention of micro- and macrovascular complications associated with the disease (Fletcher et al., 2002). Microvascular complications are disease in the small blood vessels, while macrovascular complications are disease in the large blood vessels.

Some of the complications are serious and life-threatening conditions. According to Knudsen et al. (2017), the five most important causes of death are ischemic heart disease (mainly myocardial infarction), dementia, vascular disease of the brain (stroke), chronic obstructive pulmonary disease (COPD) and lung cancer. According to the Norwegian Institute of Public Health, cardiovascular diseases (CVD) was the disease group which caused the most deaths in Norway up to 2017 (Folkehelseinstituttet, 2018b). Of the people dying from CVD in 2017, stroke was the most frequent, and myocardial infarction the second most frequent reason (Folkehelseinstituttet, 2018a).

Acute myocardial infarction is the medical name for a heart attack. The cause may be a blockage in one or more of the coronary arteries, and the blood flow to the heart muscle is abruptly cut off, causing tissue damage (Macon, Yu, & Reed-Guy, 2017). A myocardial infarction may lead to chest pain, shortness of breath, nausea, dizziness and a fast heart rate.

A stroke occurs when the blood supply to a part of the brain is interrupted or reduced. The cause may be a blocked artery (ischemic stroke) or the leaking of bursting of a blood vessel (hemorrhagic stroke). Some people may experience only a temporary disruption of blood flow to the brain (transient ischemic attack) that does not cause any permanent damage (Norsk Helseinformatikk & Norsk Elektronisk Legemiddelhåndbok, 2018b). A stroke may lead to trouble with speaking, paralysis or numbness of the face, arm or leg, and trouble with seeing in one or both eyes.

Another diabetes-related complication is foot disease caused by nerve damage or poor circulation. Foot disease caused by diabetes may result in amputation, which is the removal of a body part (Diabetesforbundet, 2018b). The most common cause of amputation in patients with diabetes is peripheral vascular disease. Amputations due to diabetes is, according to the Norwegian Directorate of Health (Helsedirektoratet, 2018a), a result of lacking/delayed preventive treatment in the primary health care service, and/or delayed referral to the specialist health care service. According to the national quality indicator, 2.1 out of 1,000 patients using blood sugar lowering drugs in Norway had to amputate a toe, foot or leg due to diabetes in 2018 (Helsedirektoratet, 2018a).

2.5 Treatment

According to the Norwegian Diabetes Association (Diabetesforbundet, 2018a), there are four factors to be highlighted when it comes to treatment. This is knowledge (and motivation), diet, physical activity and medications. Learning and having information about the disease are equally important and necessary in achieving proper self-care. Also, weight loss is a part of the treatment. For approximately 70% of the patients with T2DM, blood-sugar lowering pills or insulin are required (Diabetesforbundet, 2016a). There are a lot of medications for treating diabetes, and there are different medications for different types of diabetes. The main treatment is insulin or antidiabetic drugs, and Table 1 presents the glucose-lowering drugs in Norway (Felleskatalogen, 2019a). In addition, there are 12 drugs which includes different combinations of oral blood glucose-lowering agents.

Table 1: Overview of glucose-lowering drugs

Class	Generic name	Mechanism of action
Biguanide	*Metformin* (Glucophage)	Reduce the production of glucose by the liver
Sulfonylurea	*Glibenclamide* (Glibenclamid ratiopharm) *Glipizid* (Mindiab) *Glimepiride* (Amaryl)	Stimulate the pancreas to produce more insulin
Alpha-glucosidase inhibitor	*Acarbose* (Glucobay)	Slow the absorption of carbohydrates (sugar) ingested
Thiazolidinedione (TZD)	*Pioglitazone* (Actos)	Increase insulin sensitivity of the body cells and reduce the production of glucose by the liver
Dipeptidyl-peptidase-4 (DPP-4) inhibitors	*Sitagliptine* (Januvia) *Vildagliptin* (Galvus) *Saxagliptine* (Onglyza) *Linagliptine* (Trajenta)	Intensify the effect of intestinal hormones (incretins) involved in the control of blood sugar
Glucagon-like peptide-1 (GLP-1) agonist	*Exenatide* (Byetta) *Liraglutide* (Victoza) *Lixisenatide* (Lyxumia) *Dulaglutide* (Trulicity) *Semaglutide* (Ozempic)	Mimic the effect of certain intestinal hormones (incretins) involved in the control of blood sugar
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	*Dapagliflozine* (Forxiga) *Canaglifozine* (Invokana) *Empagliflozine* (Jardiance) *Ertugliflozine* (Steglatro)	Help eliminate glucose in the urine

Although there are costs associated with the drugs, the greatest economic burden of T2DM is the treatment of diabetic complications, which can be reduced with effective management of the disease. In addition, some of the blood-sugar lowering drugs can cause side effects, which has additional costs associated to them.

2.5.1 Side effects

According to Felleskatalogen, a Norwegian webpage including an overview of all drugs marketed in Norway, the most common side effects for SGLT2 inhibitors are hypoglycemia, vulvovaginitis, balanitis and related genital infections, polyuria (increased urinary excretion) and urinary tract infections. In addition, there has been observed some cases of amputations of the lower limb in the use of SGLT2 inhibitors. For Dapagliflozine, Empagliflozine and Ertugliflozine the following text is present in Felleskatalogen (Felleskatalogen, 2019b):

Lower limb amputations: Increased incidence of lower limb amputations (mainly toes) has been seen in long-term studies with another SLGT2 inhibitor. Unknown if this is a class effect. It is important to guide patients on routine preventive foot care.

For Canagliflozin, the following text is present (Felleskatalogen, 2019c):

Lower limb amputations: In type 2 diabetes and proven cardiovascular disease (CVD), or at least 2 risk factors for CVD, it is seen about 2 times higher risk of amputation in lower limbs (mainly toes and midfoot) in canagliflozin therapy. Risk factors are unknown. Before starting treatment, risk factors for amputation in the patient's medical history should be considered. At higher risk of amputation, careful monitoring should be considered, and the patient should be informed of the importance of routine preventive foot care and adequate hydration. In conditions that may cause amputation, such as skin ulcer, infection, osteomyelitis or lower limb gangrene, discontinuation should be considered.

2.6 Disease Management

According to the European Association for the Study of diabetes (Davies et al., 2018), the goals of treatment for T2DM are to prevent or delay complications and maintain quality of life. To do that, control of glycaemia is of high importance. According to the Norwegian directorate of Health, the first line drug-treatment of T2DM in Norway is Metformin to lower blood sugar. In cases of insufficient effect of Metformin alone, or cases where Metformin is not appropriate, individualized treatment with other blood glucose-lowering medicinal products is suggested. For most patients with T2DM, the following are suggested as second choice (not in priority order): Sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 analogs or Basal insulin (Helsedirektoratet, 2018b).

Which antidiabetic drug to use, depends on different factors. The different medication classes have different mechanism of action, and in some cases, clinical characteristics suggests the use of a particular medication. Ultimately, patient preferences are the major driving factor in the choice of medication, regarding route of administration, injection devices and side effects (Davies et al., 2018).

According to the European Association for the Study of diabetes, it is recommended that providers consider the risk of having CVD early in the process of treatment selection (Davies et al., 2018). According to the Norwegian Directorate of Health, examination to detect CVD should only be done by clinical suspicion of such disease (Helsedirektoratet, 2018c).

2.7 National Health Care system and National Reimbursement Scheme

The national health care in Norway is owned and funded by the state. The government is responsible for providing health care to the population, in accordance with the stated goal of equal access to health care. The coverage in Norway is universal and automatic for all residents by the National Insurance Scheme (Folketrygden, NIS), regardless of age, race, gender, income or area of residence. It is financed through national and municipal taxes, in addition to income-related employee and employer contributions and co-payments (Lindahl, 2016). The primary health and social care are the responsibility of the municipalities, while the specialist care is coordinated by the four Norwegian regional health authorities.

The Norwegian directorate of Health has one supervisor for health economic analysis within the health care sector (Helsedirektoratet, 2012), and one for how health effects can be included in socioeconomic analysis of measures in other sectors (Helsedirektoratet, 2018c). The general reimbursement of approved pharmaceuticals guarantees at least partial refund to the patients and is managed by the Norwegian Medicines Agency (NoMA) (Norwegian Medicines Agency, 2017).

3 Theoretical framework

3.1 Economic evaluation

According to Drummond, Schulpher, Claxton, Stoddart, and Torrance (2015), economic evaluation is defined as "*the comparative analysis of alternative courses of action in terms of both their costs and consequences".* Economic evaluation seeks to inform the range of very different, but unavoidable decisions in health care. It deals with both the inputs and outputs, and in addition concerns itself with choices. With the aim to determine the optimal course of action given the best evidence available, the outcomes of two alternatives are compared. Economic evaluation is related to scarce resources, as the resources needs to be allocated in a way that ensures as much benefit as possible. Our consequent inability to produce all desired outputs, makes the efficiency of resource allocation and the benefits of alternative treatments important (Drummond et al., 2015).

3.1.1 Types of economic evaluation

Economic evaluation can take form in three different analysis: cost-benefit (CBA), cost-effectiveness (CEA) and cost-utility (CUA). All of these examine both costs and consequences of health interventions. The main difference between these techniques is the expression of the health effect (Drummond et al., 2015). For illustration, in CBA the costs and effects are expressed in monetary terms, in CEA the effects are expressed in natural units (like life years gained), whereas in CUA the effects are expressed in a generic measure of health gain (often quantified in quality-adjusted life years (QALYs)).

3.1.2 Health outcomes / effect measure

According to Drummond et al. (2015), Norwegian Medicines Agency (2017) and the Norwegian directorate of Health (Helsedirektoratet, 2012) QALYs is the preferred measure of health gain when conducting economic evaluations. QALY is a generic measure that reflects the state of health comprising an element of the length of life as well as health-related quality of life (HRQoL). HRQoL is a measure on how the individual's well-being may be affected by a disease, disability or disorder. QALY indicates that one year of life with sickness, illness or disabilities has varying degrees of quality, compared to one year without corresponding problems. The degree of quality reduction is given by a numeric expression. 1 QALY

represents perfect health for one year, and 0 represents death. However, in some cases values below 0 is possible. The advantage of the QALY as a measure of health output is that it can simultaneously capture gains from reduced morbidity and reduced mortality, and integrate these into a single measure (Drummond et al., 2015). This is of benefit to the budget holders and decision-makers because it helps to determine the *opportunity costs*. Opportunity costs can be defined as the value of benefits of other alternatives that have been foregone by using resources on the alternative in question (Drummond et al., 2015).

There are numerous generic and specific utility instruments that evaluate the HRQoL values with a corresponding weight. Utility is used in a general sense to refer to the preferences individuals or society may have for any particular set of health outcomes. According to a review of cost-utility analysis, the two most used systems are the European Quality of Life 5 dimensions (EQ-5D) and the Short-Form 6-Dimension (SF-6D) (Wisløff et al., 2014), and according to Norwegian Medicines Agency (2017) the EQ-5D is preferred. In this thesis, EQ-5D is used. Please see section 4.2.4 for more details.

3.1.3 Cost measures

Each cost has to be identified, which means finding the costs that are relevant for the intervention of interest. The costs needs to be adjusted for differential timing, which means that the costs should be discounted if they occur in the future (Drummond et al., 2015). In a health-care perspective, only the resources used by the health care sector are counted. Also, the opportunity costs can be thought of in terms of other treatments/interventions foregone (Drummond, Weatherly, & Ferguson, 2008). Please see section 4.2.5 for more details on the costs included in this CUA.

3.1.4 Decision making

A CEA estimates the costs and the health gains of different interventions. The analysis typically looks at the costs and health gains on a control group, compares it with the intervention, and provides a method for prioritizing the allocation of resources. The CEA becomes a CUA when we determine effects in terms of utilities, and especially quality of life.

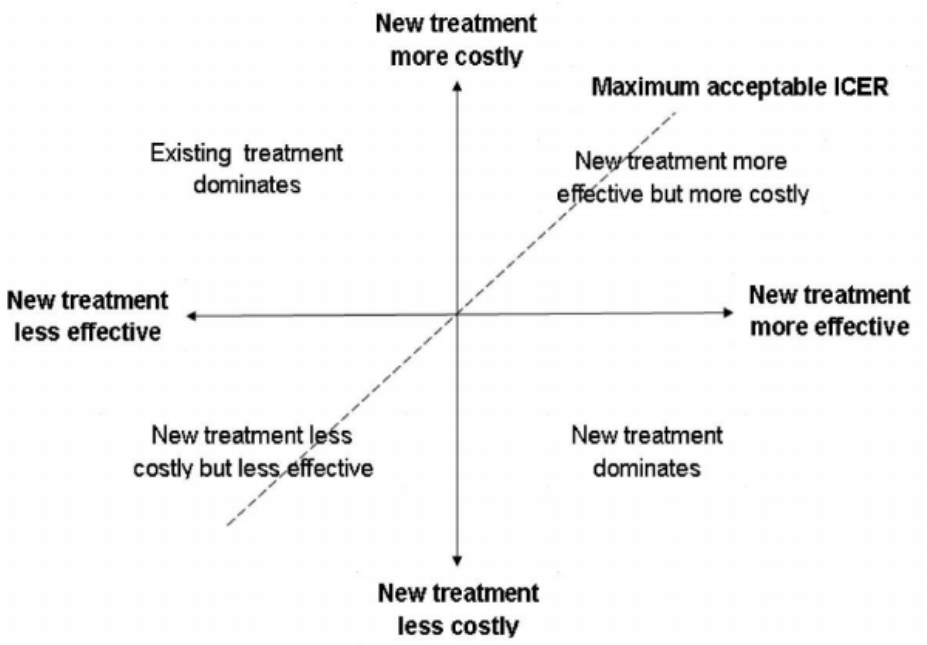
The primary interest of the CUA is the incremental cost-effectiveness ratio (ICER) given in Equation [1]. The ICER is the difference in the costs divided by the difference in the effect.

The formula looks like this:

$$\text{ICER} = \frac{\text{Cost of intervention group} - \text{Cost of control group}}{\text{Effect of intervention group} - \text{Effect of control group}} = \frac{\text{Incremental cost } (\Delta C)}{\text{Incremental effect } (\Delta E)} \qquad [1]$$

The ICER expresses the incremental cost to gain an additional unit of QALY. The most common scenario is that a new strategy improves clinical results at increased costs, and the ICER is compared to the decision rule set by the willingness to pay (WTP) per QALY obtained. The ICERs are often illustrated in a cost-effectiveness plane, as the example shown in Figure 1 (Hounton & Newlands, 2012).

Figure 1: Cost-effectiveness plane



The comparator is located in the origin. The other strategies can be more costly and more effective (north-east), less costly and more effective (south-east), less effective and more costly (north-west), or less effective and less costly (south-west) than the comparator. In case of a negative ICER, the evaluated intervention is either dominant or dominated. When an intervention is considered dominant, it means that it yields more health gain for smaller costs (south-east). In contrary, a dominated ICER refers to an intervention with less health benefits at higher costs (north-west) (Drummond et al., 2015).

3.1.5 WTP threshold

The WTP threshold per unit of effect is illustrated by the dotted line going through the origin denoted "Maximum acceptable ICER" in Figure 1. Here, strategies falling below this line are considered cost-effective. As WTP increases, the line pivots around the origin in a counter-clockwise fashion. The intervention is deemed cost-effective if the incremental costs (ΔC) divided by the incremental benefits (ΔE) are lower than the WTP per unit of effect (λ), as show in the following Equation:

$$\frac{\Delta C}{\Delta E} < \lambda \qquad [2]$$

The WTP threshold value varies across different countries. In Norway, the WTP threshold highly depends on the level of severity in addition to the opportunity cost. The Norheim Commission and the Magnussen Working Group proposed an opportunity cost of NOK 275,000 per healthy life year (NOU 2014:12, 2014). The Norwegian Government supports the commission's and the working group's assertion, although there is a significant uncertainty concerning this number. The Magnussen working group proposed that the minimum threshold value should equal the opportunity cost, and that the maximum threshold value should be three times higher, hence the threshold value should be between NOK 275,000 and NOK 825,000 (Magnussen Working Group, 2015). In addition, the working group proposed six severity classes with different weights between 1 and 3, to be multiplied with the opportunity cost (Table 3, Magnusssen Working Group). A method for measuring the level of severity, the absolute shortfall, is found in NoMA´s guidelines for submission of documentation for single technology assessment (STA) of pharmaceuticals (Norwegian Medicines Agency, 2017), and are used to find the weight number to be multiplied with the opportunity cost.

1. Define the mean age at the start of treatment in the patient group
2. Estimate the number of remaining healthy life years for an average person from the general population
3. Estimate the number of remaining healthy life years for a group of patients with the disease
4. The absolute shortfall is the difference between the estimate in part 2 and 3

Please see section 4.1.7 for the calculation of threshold value used in this thesis.

3.2 Markov model

A Markov model is a useful tool, when the decision problem involves risk over time, when the timing of event is important, and when events may happen more than once (Hunink et al., 2014). The model includes mutually exclusive and collectively exhaustive states, such as T2DM, different diabetes-related events and death. The cohort enters the model and remains in the health state for at least one cycle. One cycle is a defined period of time, for example one year or one month. At the end of a cycle, a person in the cohort can either remain in the same health state or move to another, which depends on the structure of the model and the transition probabilities. An absorbing state is a state where the probability of exiting from the state equals zero (Hunink et al., 2014). What is often called the "Markov assumption", is that the Markov model does not record the history of an individual (Drummond et al., 2015).

3.3 Sensitivity analysis

Sensitivity analysis is a way to analyze the impact of uncertainty. A sensitivity analysis attempts to quantify the impact of uncertainty on outputs of a model.

3.3.1 Deterministic sensitivity analysis

Deterministic sensitivity analysis (DSA) is a tool to examine the variation in certain input parameters or a set of parameters on an outcome. The chosen parameters are changed manually within a pre-set range, and the effect of the change is analyzed.

3.3.2 Probabilistic sensitivity analysis

Due to some limitations of DSA in providing the assessments necessary for decision-making, probabilistic sensitivity analysis (PSA) should be created to characterize parameter uncertainty. This approach is recommended by NoMA when assessing cost-effectiveness of medications (The Norwegian Medicines Agency, 2012), as a well conducted PSA will provide a more realistic representation of variations in the model results.

The first step of PSA is to express the uncertainty associated with each parameter. A probability distribution for each input parameter is defined, providing a full range of values that the parameter potentially can take, together with the probability of each value. The second step involves simultaneously selecting a probabilistic value from each parameter, and running the

model based on the selected vector of values to provide a single estimate of output. This is then repeated a large number of times, often 1,000 times, providing a distribution of outputs.

3.3.3 Cost-effectiveness acceptability curve

Cost-effectiveness acceptability curves (CEAC) is a graph that represents the probability of being cost-effective for different treatment options. This can be estimated by identifying the total costs (C) and total effect (E) for each of the 1,000 iterations derived from a PSA.

The net monetary benefit (NMB) is often estimated for a particular cost-effectiveness threshold (λ), giving Equation [3].

$$NMB = \lambda * \text{Effect} - \text{Cost} \qquad [3]$$

The probability of being cost-effective for a particular threshold is then equivalent to the proportion of the 1,000 iterations for which each treatment option has the highest net benefit (Barton, Briggs, & Fenwick, 2008). The probability of being cost-effective for each treatment will be calculated for a range of WTP threshold values and presented as a graph.

In addition to the CEAC, a cost-effectiveness acceptability frontier (CEAF) is often created to easier identify the treatment option that is expected to be cost-effective. In contrast to the CEAC, the CEAF only includes the cost-effective part of treatment options for a range of WTP thresholds. Both the CEAC and CEAF are used to communicate decision uncertainty concerning the most cost-effective choice.

4 Methods

4.1 Modelling

4.1.1 Markov model

In order to compare the cost-effectiveness of SGLT2 inhibitors with oGLD a state transition Markov model is adopted. A Markov model makes it easier to follow a cohort through time, compared to decision trees, since time is explicitly defined in the model (Briggs, Claxton, & Sculpher, 2006). The model includes 8 mutually exclusive health states. The cohort enters the model in the health state ´Type 2 diabetes mellitus´ and remains in the health state for at least one cycle. One cycle is a defined period of time and in this model one cycle equals one year. At the end of each cycle a person in the cohort either remain in the same state or move to another health state, depending on the transition probabilities. In this model, the health state "Death" is the only absorbing state. Costs and health effects are assigned to each health state in the Markov model, and is multiplied with the sample in the given health state. The Markov model simulates the consequences of having T2DM adjunct to standard of care, and the intervention.

Figure 2: Markov model

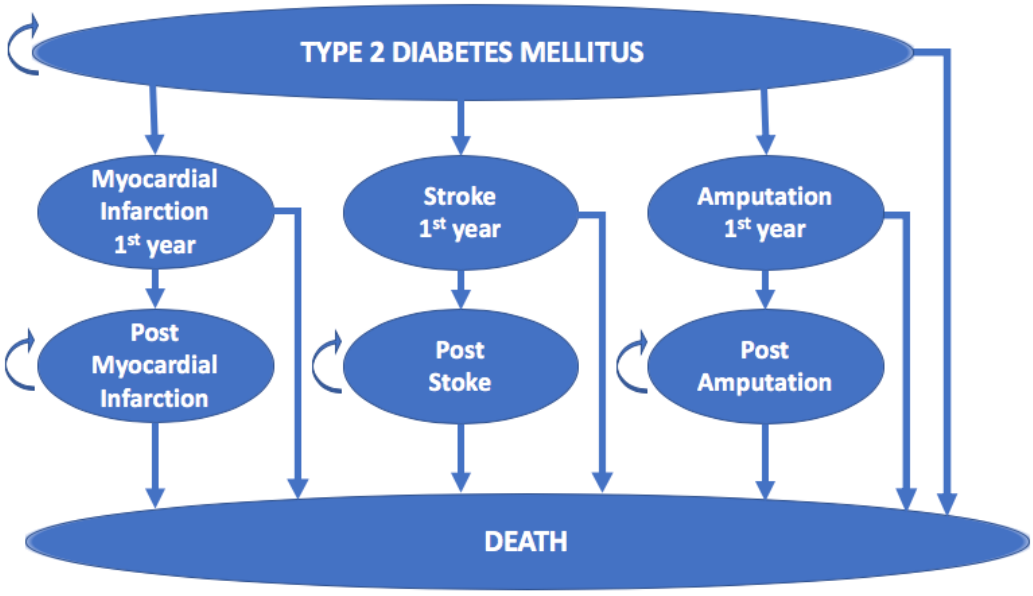


Figure 2 shows the design of the Markov model. As explained above, all patients start in the health state ´Type 2 diabetes mellitus´ and remains in the health state for at least one cycle. In addition to remain in the health state, it is possible to move from T2DM to myocardial infarction, stroke, amputation or death.

Key assumptions

This cost-utility study of the glucose-lowering drugs is based on assumptions in relation to the structure of the model and model inputs. The Markov model represents reality in a simplistic way and the following assumptions are made:

- All patients start in the health state ´Type 2 diabetes mellitus´
- A patient will be in one health state per cycle
- A patient will transit to another health state once per cycle
- The probability of progressing further or dying is irrespective of the time spent in a cycle (Markov assumption)
- It is not possible to remain in the states ´Myocardial infarction 1st year´, ´Stroke 1st year´ and ´Amputation 1st year´ more than one cycle
- It is not possible to have more than one myocardial infarction, stroke or amputation per person
- It is not possible to move between the myocardial infarction, stroke and amputation states
- The model does not differentiate between the minor and major outcomes from myocardial infarction and stroke
- The health states ´Amputation 1st year´ and ´Post Amputation" only include lower extremity amputations

4.1.2 Perspective

The analysis perspective is the healthcare provider perspective, which solely reflects the health outcomes that are experienced by the patient, and direct medical costs that entail health service provision in relation to the treatment strategy. Only the direct costs due to treatment and medication are included. Hence, costs of time traveling to the hospital, loss of working hours etc. are not included.

4.1.3 Target population

This CUA analysis is based on a cohort of patients with T2DM. Target population consists of females and males at age 60-100 years. All patients are 60 years when they enter the model, and all of them are new users of SGLT2 inhibitors with broad cardiovascular risk profile (Birkeland et al., 2017). The patients observed in the analysis are from Denmark, Norway and Sweden, using data from population-level registries with full record of disease history and mortality causes.

4.1.4 Health outcomes

The primary health outcome of this analysis is QALYs. In addition, LYs gained is presented.

4.1.5 Comparator

The comparator in this CUA is the standard of care: the use of other glucose-lowering drugs. That is insulin, metformin, sulfonylureas, DPP-4 and GLP-1.

4.1.6 Intervention

In this analysis the intervention is the use of SGLT2 inhibitors in addition to standard of care.

4.1.7 WTP threshold

As explained in section 3.1.5, the WTP threshold value is estimated by using the opportunity cost, and the severity of the disease. The severity is calculated by following the method explained in section 3.1.5, where "healthy life years" are estimated by QALYs. In practice the estimation of severity is done as follows: The mean age at the beginning of the treatment is 60 years. The estimated remaining lifetime for an average 60-year-old person from the general population is 24.9 years (Statistisk Sentralbyrå, 2019), with an average utility value of 0.80 (Sun, Irestig, Burström, Beijer, & Burström, 2012). According to the Norwegian Medicines Agency (2017), the remaining QALYs are then 19.3 (Table 2, Appendix 4). From this number one then subtracts the estimated remaining QALY for the standard of care as estimated by the model, to get an estimate of the severity, denoted by the absolute shortfall. To find the suggested WTP, one looks to Magnussen Working Group (2015) Table 3, to find a weight to multiply with the opportunity cost of NOK 275,000 per QALY. As there is no guidance regarding threshold for life years gained, the same WTP threshold value is assumed for cost per life year.

4.1.8 Half-cycle correction

In this thesis half-cycle correction is used. Half-cycle correction method is often applied in Markov models, as a more precise reflection of reality than not applying it. In Markov models, transitions between health states are modeled to occur at the beginning or at the end of a cycle, whereas in reality, it is more likely that on average, patients will transit during the cycle. Depending on timing of transition, Markov models estimate the costs and health gains that may be either underestimated or otherwise overestimated. As a result, a half-cycle correction tackles these discrepancies so that the evaluation of costs and health outcomes are representative of changes. In this thesis, the half-cycle correction is conducted by calculating the mean of the previous and the present year.

4.1.9 Time horizon

The time horizon should be so long that all the important future differences in costs and effects between the alternatives are captured (Basu, Maciejewski, & Basu, 2019). And, since the SGLT2 inhibitors have effect on mortality, a life time perspective is used. The patients entering the cohort are 60 years old, and the time horizon is 40 years.

4.1.10 Discounting

To adjust for future costs and health outcomes, the costs and health outcomes are discounted at 4% per year. The discount rate is recommended by the NoMA (The Norwegian Medicines Agency, 2012).

4.1.11 Sensitivity analysis

Deterministic sensitivity analysis

In this thesis, a one-way sensitivity analysis is conducted, to examine the impact of utility parameters, costs in different Markov-states, changes in the different risks and change in the hazard ratios (used for calculation of new transition probabilities). A tornado plot is used to present the effects on the incremental NMB (iNMB). Each parameter is represented by a horizontal bar, which indicates the uncertainty in the iNMB associated with uncertainty in that input. The 95% confidence interval for all parameters are used as range. The parameter in which variation has the biggest impact on the study result is at the top of the horizontal bar.

Probabilistic sensitivity analysis

In this thesis, 1,000 simulations are conducted in the probabilistic sensitivity analysis. Different distributions are used to calculate the different values. For the utility and transition probabilities, the beta distribution is used. For costs, the gamma distribution is used, and for the hazard ratios and increased risks, the log-normal distribution is used.

4.1.12 Formulas

If the data is presented in probabilities and needs to be transformed to rates, Equation [4] will be used (Briggs et al., 2006). This may be the case when the probabilities should be multiplied with hazard ratios.

$$r = -[ln(1 - P)]/t \qquad [4]$$

Where p = probability, r = rate and t = time unit

After the multiplication is done, the rates need to be retransformed back into probabilities using Equation [5]. This is also the case if the rates and probabilities are not given for the same time period as the cycle length defined.

$$p = 1 - exp(-rt) \qquad [5]$$

To find the values to make PSA, a total of 7 formulas are used. If there is no confidence interval or standard deviation stated, the upper confidence interval is estimated 20% higher than the mean. The following formulas are used:

Equation [6] – Standard error from upper bounds

*St.err = (Upper bound – mean) / (2*1.96)*

Equation [7] – Standard error from two rates

St.err = Sqrt (1/a + 1/b)

Equation [8] – Standard error from a sample

*St.err = Sqrt ((p * (1-p)) / n)* **

Equation [9] – Calculating alpha to beta distribution

$$Alpha = Mean * (((mean * (1-mean)) / (st.err^2))-1)$$

Equation [10] – Calculating beta to beta distribution

$$Beta = (1-mean) * (((mean*(1-mean)) / (st.err^2))-1)$$

Equation [11] – Calculating alpha to gamma distribution

$$Alpha = Mean^2 / st.err^2$$

Equation [12] – Calculating beta to gamma distribution

$$Beta = St.err^2 / mean$$

**Sqrt = square root

4.2 Inputs and parameters

To do the analysis, it is vital to use relevant parameters. The parameters are estimates for transition probabilities, probability of dying, utility weights and costs of the health states and costs of SGLT2 inhibitors.

Patients with T2DM having a myocardial infarction, stroke or amputation, do have higher probability of dying compared to people without diabetes. In addition, the risk of dying is higher the first year after having a myocardial infarction, stroke and amputation. At the same time, the described conditions lead to lower health-related quality compared to not having the conditions, and this is taken into account in the analysis. This is estimated through QALYs for all health states in the model. In addition to transition probabilities, probability of dying and utility weights, the costs are estimated.

4.2.1 Transition probabilities

Probabilities for different outcomes are essential for the Markov model, as they lead the distribution of people to the different health states. In this Markov model, all patients start in the health state named ´Type 2 diabetes mellitus´. A patient can after one year (in the next cycle) move to the health states ´Myocardial infarction 1st year´, ´Stroke 1st year´, ´Amputation 1st year´ or ´Death´, or the person can stay in the original health state. The following year the

same thing may happen, and all patients having a myocardial infarction, a stroke or an amputation are moved to the following health states respectively: ´Post myocardial infarction´, ´Post stroke´, ´Post amputation´ or ´Death´. It is not possible to stay in the ´Myocardial infarction 1st year´, ´Stroke 1st year´ and ´Amputation 1st year´ states more than one cycle. The transition probabilities from ´Type 2 diabetes mellitus´ to the different health states for patients using oGLD are presented in Table 2.

Table 2: Transition probabilities from health state ´Type 2 diabetes mellitus´ to different health states

Health state	Value	Distribution	Source
Myocardial infarction 1st year	0.077	Beta	Birkeland et al (2017)
Stroke 1st year	0.066	Beta	Birkeland et al (2017)
Amputation 1st year	0.004	Beta	Birkeland et al (2017)

The transition probabilities presented in Table 2 are found in the observational analysis CVD-REAL Nordic (Birkeland et al., 2017), by dividing he number of events by the number of people in the control group.

4.2.2 Hazard ratios

For patients using the SGLT2 inhibitors, the transition probabilities for myocardial infarction and stroke are calculated using hazard ratios from the systematic review and meta-analysis of cardiovascular outcome trials (Zelniker et al., 2019). Zelniker et al. includes three trials in the meta-analysis; CANVAS Program, DECLARE-TIMI 58 and EMPA-REG Outcome. The values of the hazard ratio used are presented in Table 3.

Table 3: Hazard ratios used to calculate transition probabilities from health state ´Type 2 diabetes mellitus´ to different health states using SGLT2 inhibitors

Health state	Value (95% CI*)	Distribution	Source
Myocardial infarction 1st year	0.89 (0.80-0.98)	Log-normal	Zelniker et al. (2019)
Stroke 1st year	0.97 (0.86-1.10)	Log-normal	Zelniker et al. (2019)
Amputation 1st year	1.29 (0.87-1.92)	Log-normal	Random effect Meta-analysis

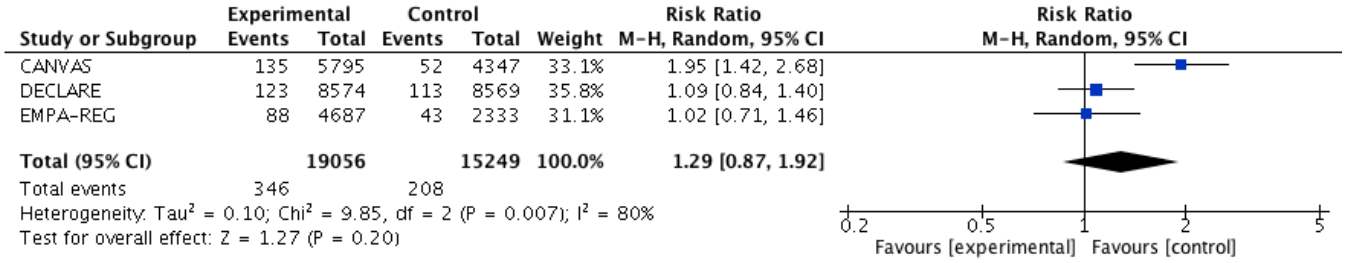
*CI: Confidence Interval

The transition probabilities for the different health states using oGLD, are transformed into rates using Equation [4] and multiplied with the hazard ratios for each event. Then, Equation [5] is used to retransform back into probabilities. For the probabilistic sensitivity analysis, beta

distribution is used on the transition probabilities for patients using oGLD, using alpha and beta from Birkeland et al (2017). Equation [6] is used on the hazard ratios to calculate the standard error from the 95% confidence interval, and log-normal distribution is used to estimate the probabilistic values.

The hazard ratio for amputation is calculated by making a random-effects meta-analysis, in the program Review Manager 5.3. The same three trials used in Zelniker et al.´s meta-analysis are used; EMPA-REG OUTCOME (Zinman et al., 2015), CANVAS (Neal et al., 2017) and DECLARE (Wiviott et al., 2019). In addition, an article written by Inzucchi et al. about amputations in EMPA-REG was used (Inzucchi, Iliev, Pfarr, & Zinman, 2018). The number of amputations and number of people in the control group are used to estimate the new hazard ratio. Figure 3 presents the meta-analysis inputs and outputs for the new hazard ratio.

Figure 3: Random-effect meta-analysis



By making the random effect meta-analysis, the hazard ratio for amputations with SGLT2 inhibitors is estimated to be 1.29 (95% Confidence Interval: 0.87-1.92). To calculate the probability of having amputation using SGLT2 inhibitors, the transition probability for amputation using oGLD is transformed into rate using Equation [4], multiplied with 1.29 and retransformed back into probability with Equation [5]. For the probabilistic sensitivity analysis, Equation [6] is used to calculate the standard error from the 95% confidence interval, and log-normal distribution is used to estimate the probabilistic values.

4.2.3 Mortality

In this analysis, a patient entering the model is 60 years old, having either SGLT2 inhibitors or oGLD, as treatment for T2DM. A person having a stroke, a myocardial infarction or amputation often have higher probability of dying within the first year than the following years,

and this is taken into account in the model. Table 4 presents the probability of dying within the first year for different health states, and they are assumed to be independent of age.

Table 4: Probability of dying the first year after an event, from different health states

Health states	Value	Distribution	Source
Myocardial infarction 1st year	0.203	Beta	Statistics of Norway (2017) and Ariansen (2014)
Stroke 1st year	0.213	Beta	Statistics of Norway (2017) and Ariansen (2014)
Amputation 1st year	0.30	Beta	Statistics of Norway (2017) and Thorud (2016)

For the probability of dying from T2DM and the probabilities of dying from the health states ´Post myocardial infarction´, ´Post stroke´ and ´Post amputation´, age is taken into account. Please see Appendix for the probabilities of dying for all ages. Table 5 presents the increased risks used to calculate the probability of dying from T2DM and the post-health states.

Table 5: Increased risk of dying from T2DM, myocardial infarction and stroke

Event	Value	Distribution	Source
Type 2 diabetes mellitus	1.588	Log-normal	Zghebi et al. (2017)
Myocardial infarction	2.421	Log-normal	Majed et al. (2015)
Stroke	4.009	Log-normal	Majed et al. (2015)

Type 2 diabetes mellitus

To calculate the probability of dying from T2DM, the probability of dying for ages 60 to 100 found in ´Table of mortality´ at Statistics Norway (Statistikkbanken, 2017), with the mean estimate for the population as a whole, are used. Firstly, they are transformed into rates with Equation [4] and multiplied with the increased risk of dying by having T2DM (1.588) compared to a person without diabetes. The rates are then retransformed back into probability by using Equation [5]. The increased risk is estimated from mortality rates found in an article looking at trends in T2DM incidence, prevalence and mortality in the United Kingdom between 2004 and 2014 (Zghebi et al., 2017). The probability of dying for a 60-year-old is used in the first year of the Markov model, and is adjusted to 60 + the number of years following. Thus, the annual probability of dying will increase in line with the increasing age in the model. Please see Appendix for the probabilities of dying for patients with T2DM, given different ages. For the probabilistic value, a log-normal distribution of the increased risk (1.588) is used. Equation [7] is used with number of deaths in each group as *a* and *b*.

For patients using SGLT2 inhibitors, the probabilites of dying found for patients using oGLD is transformed into rate using Equation [4] and then multiplied with the hazard ratio for all-cause mortality from the systematic review and meta-analysis of cardiovascular outcome trials (Zelniker et al., 2019), which equals 0.85 (95% CI: 0.78-0.93). Then it is retransformed back into probability by using Equation [5]. Please see Appendix for all the probabilities of dying from T2DM using SGLT2 inhibitors, given different ages. For the probabilistic sensitivity analysis, Equation [6] is used to calculate the standard error from the 95% confidence interval, and log-normal distribution is used to estimate the probabilistic values.

Myocardial infarction

The probability of dying from ´Myocardial infarction 1st year´ is found to be 20.3%. The value is found by using the number of patients who had an outpatient consultation or entered hospitals in 2016 for myocardial infarction (11,401) at Norwegian Institute of Public Health's webpage (Ariansen, Egeland, Graff-Iversen, Sakshaug, & Selmer, 2014). According to Statistics of Norway, 2,314 people died from myocardial infarction in 2016. By dividing the number of patients who died on the number of patients with myocardial infarction the same year, the result presents an estimate of the probability of dying within the first year (20.3%). The probability of still being alive and move to the health state ´Post myocardial infarction´ (1 – 0.203 = 0.797) is 79.7%. Probabilistic value is found by using beta distribution with alpha and beta values from the article.

The probability of dying from the health state ´Post myocardial infarction´, is estimated by calculating the increased risk of dying by having a myocardial infarction, compared to not having myocardial infarction. This is calculated by using values from a paper by Majed et al. (2015). They investigated the all-cause mortality risk up to and after coronary heart disease (CHD) and stroke in European middle-aged men. The mean age in the paper is 55 years. The paper reported the annual all-cause mortality rates per 1,000 person-years up to and after CHD and stroke, over 10 years of follow-up. The mortality rate after CHD is divided by the mortality rate up to CHD, which equals 2.421, and is an estimate of the increased mortality after CHD. The increased risk is multiplied with the rate of all-cause mortality for T2DM, for each age (other glucose-lowering drugs and SGLT2 inhibitors rate), which is described above. Please see Appendix for the probabilities of dying from the heath state ´Post myocardial infarction´ given age. For the probabilistic value, Equation [8] is used to calculate the standard error, and

the log-normal distribution is used on the increased risk to estimate new probabilities for all ages.

Stroke

The probability of dying from ´Stroke 1st year´ is estimated to be 21.3%. According to the Norwegian Directorate of Health (Helsedirektoratet, 2017) the annual death rate is below 25%. Data from the Norwegian register of stroke shows that 19% are dead within 90 days after a stroke, which then indicates a higher death rate after one year. According to the Norwegian Institute of Public Health (Ariansen et al., 2014) 11,330 patients had an outpatient consultation or entered hospitals in 2016 for stroke, and Statistics of Norway states that 2,416 people died from stroke in 2016. This makes 21.3% deaths within one year, which seems reasonable, and presents an estimate of the probability of dying within one year. The probability of moving to the health state ´Post stroke´ (1 – 0.213 = 0.787) is 78.7%. Probabilistic value is found using beta distribution with alpha and beta values from the article.

The probability of dying from ´Post stroke´ is also found in the paper by Majed et al. (2015). The mortality rate after a stroke is divided by the mortality rate up to a stroke, which equals 4.009 and is the increased mortality after a stroke. The increased risk is multiplied with the rate of all-cause mortality for each age (for other glucose-lowering drugs and SGLT2 inhibitors). Please see Appendix for the probabilities of dying from the health state ´Post stroke´ given age. For the probabilistic values, Equation [8] is used to calculate standard error, and the log-normal distribution is used on the increased risk to estimate new probabilities for all ages.

Amputation

Table 6: Probability of dying from amputation

Year	Value	Distribution	Source
1st year	0.30	Beta	Shah et al. (2013)
2nd year	0.236	Log-normal	Used data from Thorud et al. (2016)
3rd year	0.118	Log-normal	Used data from Thorud et al. (2016)
4th year	0.059	Log-normal	Used data from Thorud et al. (2016)
5th year	0.030	Log-normal	Used data from Thorud et al. (2016)

According to Shah et al. (2013), the probability of dying within the first year after an amputation is 30% (95% CI: 0.26 – 0.35). The paper looks into patients who underwent lower extremity amputations including standard demographics and other clinical data, such as

presence of diabetes. The probability of moving to the health state ´Post amputation´ (1 – 0.30 = 0.70) equals 70%. Probabilistic value is found using beta distribution with alpha and beta values from the article.

The probability of dying the following years after an amputation is found by using data from a systematic review (Thorud, Plemmons, Buckley, Shibuya, & Jupiter, 2016). The paper looks into 5-year mortality after minor and major amputations in 31 studies and presents 6 studies which includes diabetes patients only. The mean age, standard deviation and 5-year mortality were calculated for the 6 studies, with the mean age equal 67.1, standard deviation equal 0.107 and the 5-year mortality equal 0.61. A log-normal age distribution was used.

By subtracting the probability of dying the first year from the 5-year mortality (0.61 – 0.30 = 0.31), the probability of dying year 2-5 after an amputation is found to be 31%. This corresponds to 44.6% of the patients that have survived the first year (0.31/0.70 = 0.446). For each year 2-5, the probability for the surviving patients is assumed to be cut in half compared with the previous year (see Table 6). An assumption made is that if a person has survived to year 6 after an amputation, the mortality of dying from amputation is equal to zero, and the mortality rate equals the probability of dying from the health state T2DM, given the different ages.

4.2.4 Utility values

In order to calculate the health outcomes of QALYs, the utility estimates need to be included. All of the utility values used are found in a review paper by Beaudet, Clegg, Thuresson, Lloyd, and McEwan (2014). The paper did a systematic literature review of diabetes and its complications, and recommended a proposed reference case in accordance with the National Institute for Health and Care Excellence (NICE) for use in economic analysis. A Norwegian paper looking into HRQoL in diabetes (Solli, Stavem, & Kristiansen, 2010) was included in the review, but the preferred utility values for modeling complications associated with T2DM, was found in a paper from the United Kingdom (Clarke, Gray, & Holman, 2002).

The utility value of having T2DM equals 0.785 in the article from Clarke et al., and 0.850 in the article from Solli et al. There are also differences in the utility values of myocardial infarction, stroke and amputation. For the preferred utility values presented in the review paper,

most of the utility values are extracted from Clarke et al., because of its large sample size, the T2DM-specific nature, the recognized strong methodological quality, and the use of the EQ-5D questionnaire (Beaudet et al., 2014). As a result of the recommendation from Beaudet et al. the values from Clarke et al. are used in this thesis.

Table 7: Utility values for different health states

Health state	Utility (95% CI*)	Distribution	Source
Type 2 diabetes mellitus	0.785 (0.681 – 0.889)	Beta	Clarke et al. (2002)
Myocardial infarction	-0.055 (-0.067 – -0.042)	Beta	Clarke et al. (2002)
Stroke	-0.164 (-0.222 – -0.105)	Beta	Clarke et al. (2002)
Amputation	-0.280 (-0.389 – -0.170)	Beta	Clarke et al. (2002)

*CI: Confidence Interval

Table 7 shows the utility values for the health state T2DM, and the diabetes-related events included in this thesis. The utility values are equal for the 1st year and the following years. The utility value of the T2DM health state is a positive value, and the diabetes-related events are presented in negative values as they are disutilities. They are therefore subtracted from the T2DM value. In the paper of Clarke et al., the EQ-5D index was used to describe how diabetes complications influence the HRQoL. The 95% confidence interval presented in the article is used with Equation [6] to find the standard deviation. Equation [9] and [10] are used to calculate alpha and beta used for the probabilistic values.

4.2.5 Costs

A person having a stroke, a myocardial infarction or an amputation often have large health expenditures the first year and lower costs in the following years. The health status of these diseases is therefore divided into two, the first year health states with costs associated with first year treatment, and the post-health states with average costs for the other years. All costs have been converted to NOK 2018, using the consumer price index (www.ssb.no/kpi), and exchange rates from Norges bank (www.norges-bank.no).

Price of SGLT2 inhibitors

A relevant cost included in the model is the costs of using SGLT2 inhibitors. The recommended daily doses of the four different SGLT2 inhibitors examined, is found using the Norwegian website Felleskatalogen. By using the NoMA medicine database (legemiddelsøk), the maximum retail price for the pharmacies were found. The four drugs examined were

Canagliflozin 100 mg and 300 mg, Empagliflozin 10 mg and 25 mg, Dapagliflozin 10 mg and Ertugliflozine 5 mg and 10 mg.

To find the costs per year of using SGLT2 inhibitors, the package size, the recommended daily dose and the price per package is used. By dividing 365 days in a year on the package size (for example 90 pills in one package), the number of packages a person would need for a year is found. This number is multiplied with the price per package to find the costs per year. After calculating costs for all four drugs, the lowest cost per year was used in the model (NOK 4,974 for Dapagliflozin 10 mg). The price found is multiplied with all health states for patients using SGLT2 inhibitors.

Costs associated with the health states

Table 8 shows the annual costs of different health states, followed by an explanation on how the estimates are found and calculated.

Table 8: Annual costs of different health states

Health state	NOK (95% Confidence Interval)	Distribution	Source
Myocardial infarction 1st year	177,395 (159,655 – 212,874)	Gamma	Hagen (2015)
Stroke 1st year	157,175 (141,457 – 188,610)	Gamma	Hagen (2015)
Amputation 1st year	101,567 (68,264 – 143,240)	Gamma	Graz (2017)
Post Myocardial infarction	10,586 (9,527 – 12,703)	Gamma	Trueman (2013)
Post Stroke	4,219 (3,797 – 5,062)	Gamma	Trueman (2013)
Post Amputation	19,066 (11,278 – 31,881)	Gamma	Graz (2017)

Myocardial infarction

The costs for the first year after a myocardial infarction are estimated at NOK 156,987 (Hagen, 2015) presented in 2013 value. Adjusting for inflation using the consumer price index, this corresponds to NOK 177,395 in 2018. There is no confidence interval given, therefore it is assumed that the upper confidence level is 20% higher than the deterministic value. Using Equation [6], standard errors are calculated, and alpha and beta for a gamma distribution are found using Equation [11] and [12].

The costs for the following years after myocardial infarction are derived from Trueman and Anokye (2013). The lifetime costs were estimated to be £ 17,728 (in 2010 value), with the estimated remaining lifetime of 18.41 years. The mean cost per year is calculated and converted into 2018 value, by using exchange rate for 2010 from the central bank of Norway and the consumer price index to estimate the 2018 value. The calculated costs in 2018 values equals NOK 10,586. There is no confidence interval given, so the upper confidence level is assumed to be 20% higher than the deterministic value. Using Equation [6], standard errors are calculated, and alpha and beta are found using Equation [11] and [12]. The probabilistic values are then derived using an inverse gamma distribution.

Stroke

The costs for the first year after a stroke are estimated at NOK 153,016 (Hagen, 2015) presented in 2013 value. The costs are transformed into 2018 value, by using the consumer price index and corresponds to NOK 157,175. There is no confidence interval given, so the upper confidence level is assumed to be 20% higher than the deterministic value. Using Equation [5], standard errors are calculated, and alpha and beta are found using Equation [10] and [11]. The probabilistic values are then derived using an inverse gamma distribution.

The costs for the following years after stroke are derived from Trueman and Anokye (2013). The lifetime costs were estimated to be £ 1,965, with the estimated remaining lifetime equal 5.12 years. The mean cost per year is calculated and converted into 2018 value with the same procedure as for myocardial infarction, which equals NOK 4,219.15. There is no confidence interval given, so the upper confidence level is assumed to be 20% higher than the deterministic value. Using Equation [6], standard errors are calculated, and alpha and beta are found using Equation [11] and [12]. The probabilistic values are then derived using an inverse gamma distribution.

Amputation

The costs for the first year after an amputation is estimated at £ 9,546 (95% CI: 6,416 – 13,463), given in 2012 value. (Graz, D´Souza, Alderson, & Graz, 2018). The costs are calculated into 2018 value, using 2012 exchange rate and equals NOK 101,567.

This estimate is strengthened by the findings of the cost of an operation, using diagnose related weights (DRG). This is estimated by using the code “amputations due to sickness in D10”,

which has a weight at 3.953 and 0.102. The mean of both weights equals 2.0275, which is multiplied with the price of one DRG-point (43,328). This equals NOK 88,050 and presents the costs only for the operation.

The costs for the subsequent years after amputation are estimated at £ 1,792 (95% CI: 1,060 – 2,943), which is calculated to equal NOK 19,066 (2018 value). As Graz et al. (2018) describes, the costs are for all types of amputations, it does not breakdown between major, minor, and procedures on amputation stumps. The costs include prosthetic services, physiotherapy sessions and wheelchair provision. The societal costs due to loss of revenue are not included in this estimates (Graz et al., 2018).

4.3 Software

The CUA and subsequent sensitivity analysis is performed in Microsoft Excel 2016. Macros used to run the PSA simulations are written in Visual Basic, with 1,000 repetitions. Review Manager 5.3 is used to develop the random-effect meta-analysis to find the new hazard ratio for amputation.

5 Results

5.1 Severity and WTP threshold

The estimated remaining QALY for patients on standard current treatment is estimated to be 9.59 (undiscounted). The absolute shortfall is calculated by subtracting the QALYs for the patients with diabetes, from the QALYs for the average 60-year-old person (19.3 – 9.59). The absolute shortfall of T2DM is therefore 9.71. The shortfall measured are within group 3 in Magnussen Working Group (2015), Table 3. The weight associated with this group is 1.80, meaning that the opportunity cost of NOK 275,000 should be multiplied with 1.8. Given this information, the chosen WTP threshold is NOK 475,000 per QALY and LY gained.

5.2 Cost-effectiveness analysis

The results from deterministic cost-effectiveness analysis are summarized in Table 9. It illustrates the overall treatment costs, QALYs and LYs gained for the new intervention compared to the standard of care. The costs are illustrated from the Norwegian health care provider's perspective.

Table 9: Cost-effectiveness results for a cohort of patients with T2DM

Undiscounted results			
Strategy	**Costs**	**QALY**	**LY**
oGLD	NOK 205,446	9.59	13.23
SGLT2i	NOK 278,359	10.18	14.08
Increment	*NOK 72,913*	*0.59*	*0.85*

Discounted results			
Strategy	**Costs**	**QALY**	**LY**
oGLD	NOK 157,482	7.12	9.75
SGLT2i	NOK 207,099	7.42	10.18
Increment	*NOK 49,617*	*0.30*	*0.42*

	Incremental cost/QALY	**Incremental cost/LY**
ICER	NOK 166,460	NOK 116,827

As Table 9 shows, the calculations give a positive incremental cost of NOK 49,617, which means that the new intervention is more costly compared to the standard care. Also, the

incremental QALYs and incremental LYs show a positive incremental effect of 0.30 QALYs and 0.42 LYs. This means that the new intervention gains higher HRQoL and more LYs compared to the standard of care. Moreover, the ICER is NOK 166,460 per QALY and NOK 116,827 per life year, which is lower than the assumed WTP threshold of NOK 475,000.

5.3 Sensitivity analysis

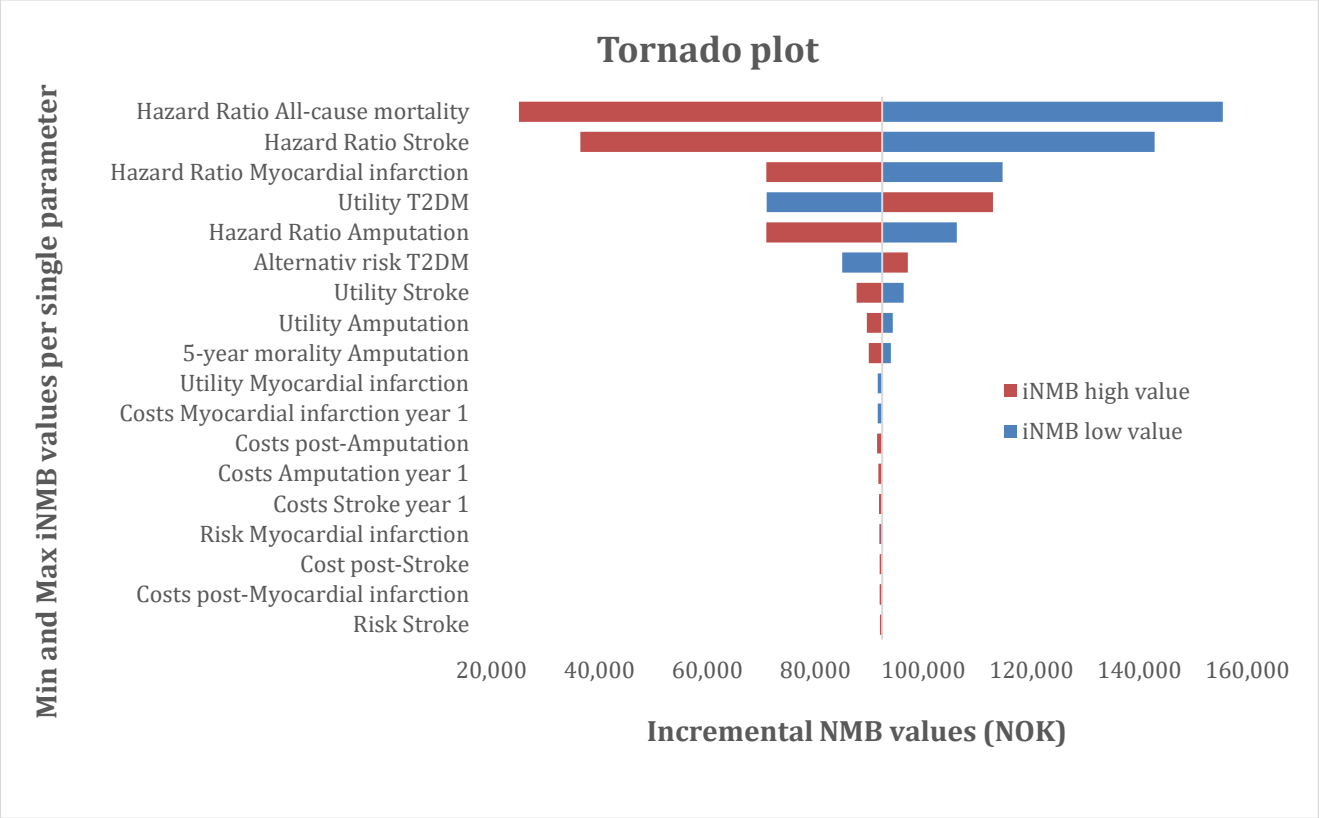
5.3.1 Deterministic sensitivity analysis

One-way sensitivity analysis

For the one-way sensitivity analysis, the net monetary benefit is estimated. The iNMB in the base case using WTP threshold of NOK 475,000, equals NOK 92,883. The base case means that all the parameters have original values.

The one-way sensitivity analysis revealed two key parameters that have great impact on the iNMB. The first parameter is the hazard ratio of SGLT2 inhibitors compared to standard treatment on all-cause mortality and the second parameter is the hazard ratio of stroke. In fact, the iNMB value ranges from NOK 25,117 to NOK 155,483. Next, there are three parameters that have medium impact on the iNMB; the hazard ratio of myocardial infarction, the utility value of having T2DM, and the hazard ratio of amputations. The utility value of having stroke, the utility value of having an amputation, and the 5-year mortality rate after amputation have even less impact of the iNMB. The results of all one-way sensitivity analysis are combined into a tornado diagram and are presented in Figure 4.

Figure 4: Tornado plot representing the results of the one-way sensitivity analysis for different parameters



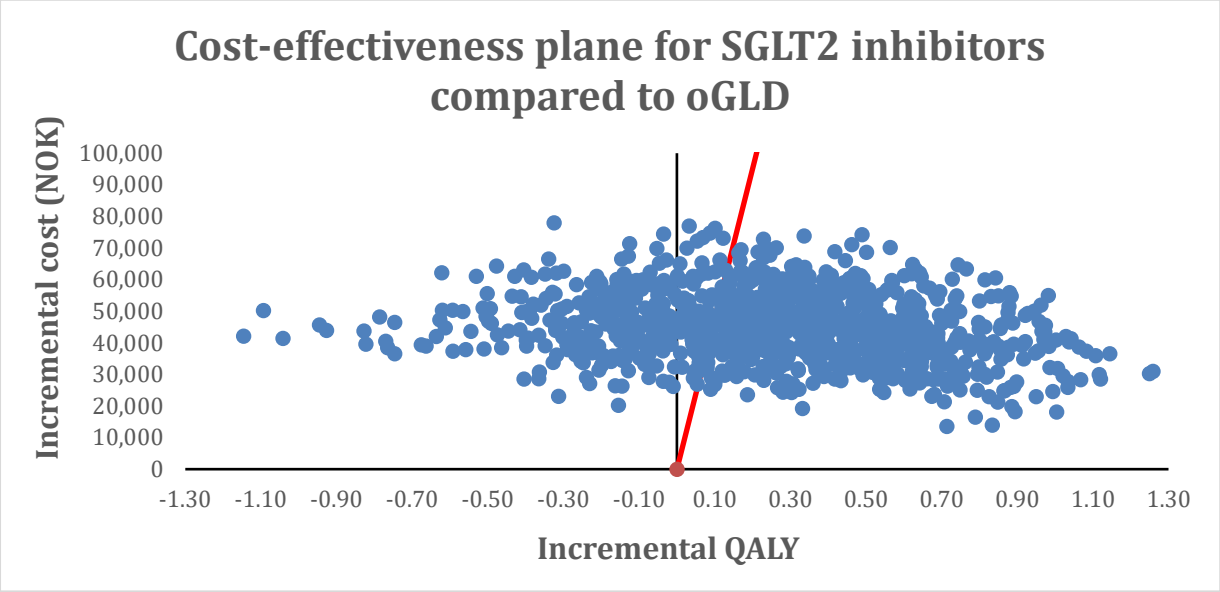
5.3.2 Probabilistic sensitivity analysis

Findings from the PSA are presented in the cost-effectiveness plane in Figure 5 and 6. As described in Section 3.1.4, the differences in effect and costs between SGLT2 inhibitors and oGLD in 1,000 ICERs are estimated.

QALYs

For the 1,000 simulation, the mean incremental cost was NOK 45,253, the mean incremental effect was 0.26 QALYs, and the mean ICER was NOK 174,050. The ICERs in the cost-effectiveness plane are distributed across two quadrants, with the majority of ICERs observed in the north-east quadrant. There are 77.1% observations in the north-east quadrant, and 22.9% observations in the north-west quadrant, indicating that the new intervention has 77.1% probability of being more costly and provide more health gain. The remaining simulations indicate a 22.9% probability that the new intervention is more costly and provides less health gain.

Figure 5: Cost-effectiveness plane, presenting costs and QALY

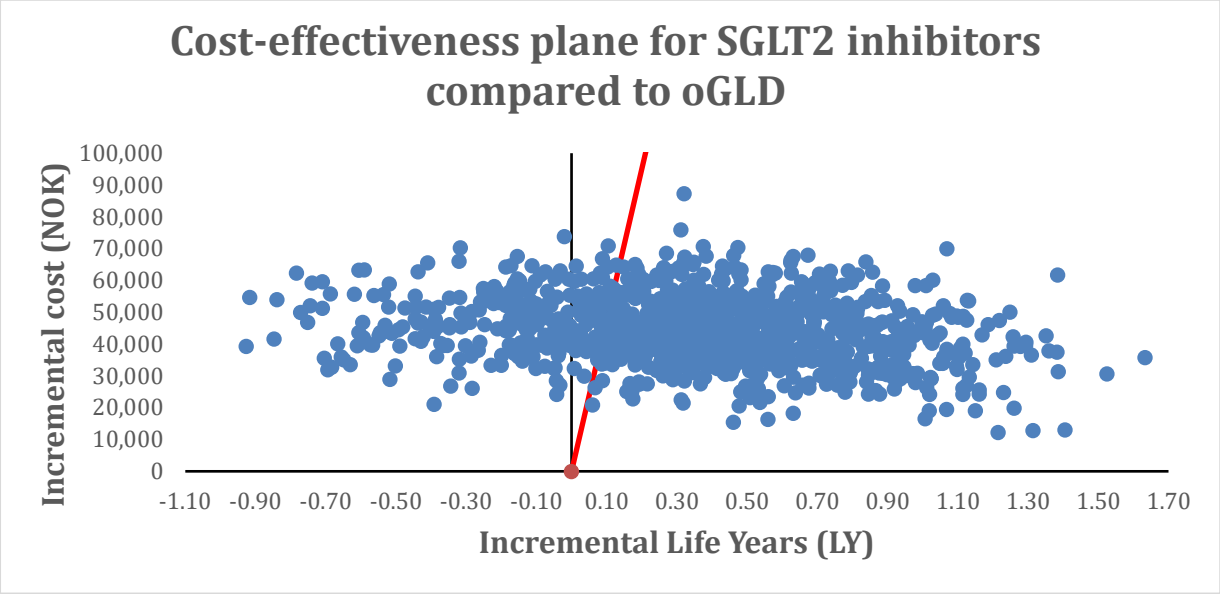


The red line indicates the WTP threshold value, equal NOK 475,000 per QALY gained. The observations at the right-hand side of the red line indicates the cost-effective observations given the WTP threshold value. The observations between the red line and the y-axis, indicates that the observations are more costly and provides more health gain compared to the standard of care, but they are not cost-effective given the WTP threshold value of NOK 475,000. Given the distribution of the ICERs from the simulations, it can be concluded that the intervention is cost-effective in 68.3% of the cases for WTP threshold of NOK 475,000. A higher WTP threshold would increase the number of cost-effective observations.

Life Years

For the 1,000 simulation, the mean incremental cost was NOK 44,685, the mean incremental effect was 0.36 LYs, and the mean ICER was NOK 124,125. The ICERs in the cost-effectiveness plane are distributed across two quadrants, with the majority of ICERs observed in the north-east quadrant, like the cost-effectiveness plane for QALYs. There are 80.4% observations in the north-east quadrant, and 19.6% observations in the north-west quadrant, indicating that the new intervention has 80.4% probability of being more costly and provide more health gain. The remaining simulations indicate a 19.6% probability that the new intervention is more costly and provides less health gain.

Figure 6: Cost-effectiveness plane, presenting costs and Life years



The red line indicates the WTP threshold value, equal NOK 475,000 per LY gained. The observations at the right-hand side of the red line indicates the cost-effective observations given the WTP threshold value. The observations between the red line and the y-axis, indicates that the observations are more costly and provides more health gain compared to the standard of care, but they are not cost-effective given the WTP threshold value of NOK 475,000. Given the distribution of the ICERs from the simulations, it can be concluded that the intervention is cost-effective in 74.3% of the cases for WTP threshold of NOK 475,000.

5.4 Cost-effectiveness acceptability curve

The results of the PSA are utilized in the NMB analysis and plotted on the cost-effectiveness acceptability curve. Figure 7 to 10 illustrates the likelihood of the standard care and the SGLT2 inhibitors treatment being cost-effective, given the value of the WTP thresholds on the horizontal axis.

QALYs

Figure 7 shows the probability of oGLD and SGLT2 inhibitors being cost-effective given different values of the WTP threshold for QALYs. The standard treatment, oGLD, is the most cost-effective treatment for WTP threshold-values up to NOK 174,050, and for values above this the intervention, SGLT2 inhibitors, is most cost-effective. The probability of being cost-effective flattens out at approximately 65%. Figure 8 shows only the cost-effective option for all WTP threshold values.

Figure 7: Cost-effectiveness acceptability curve for QALY

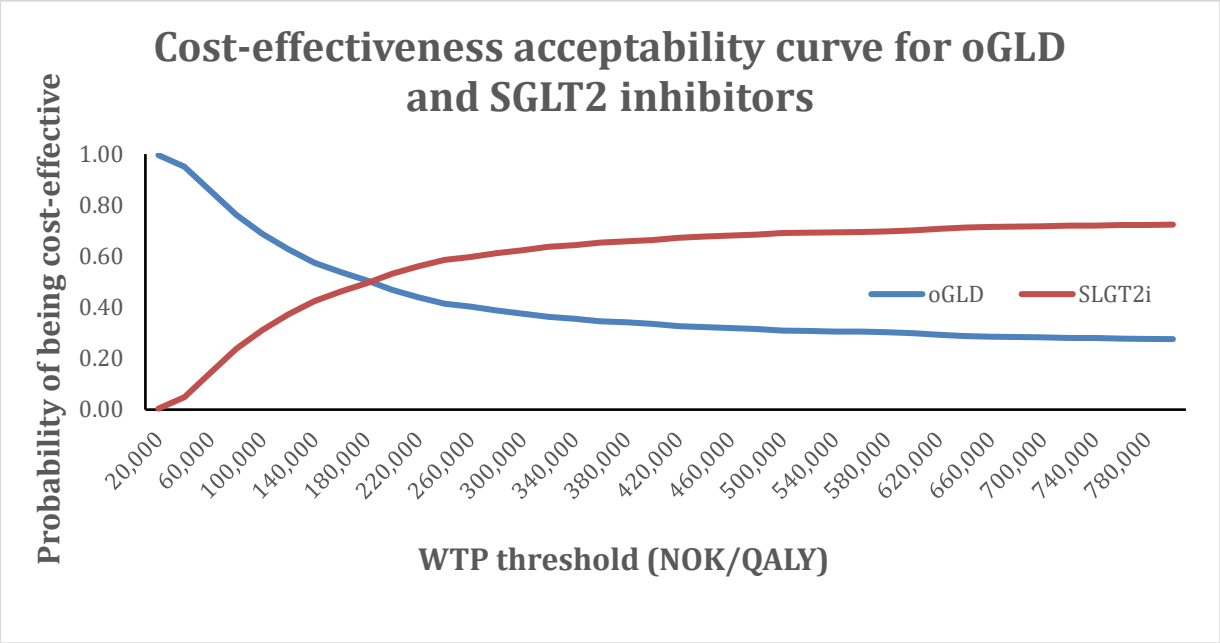
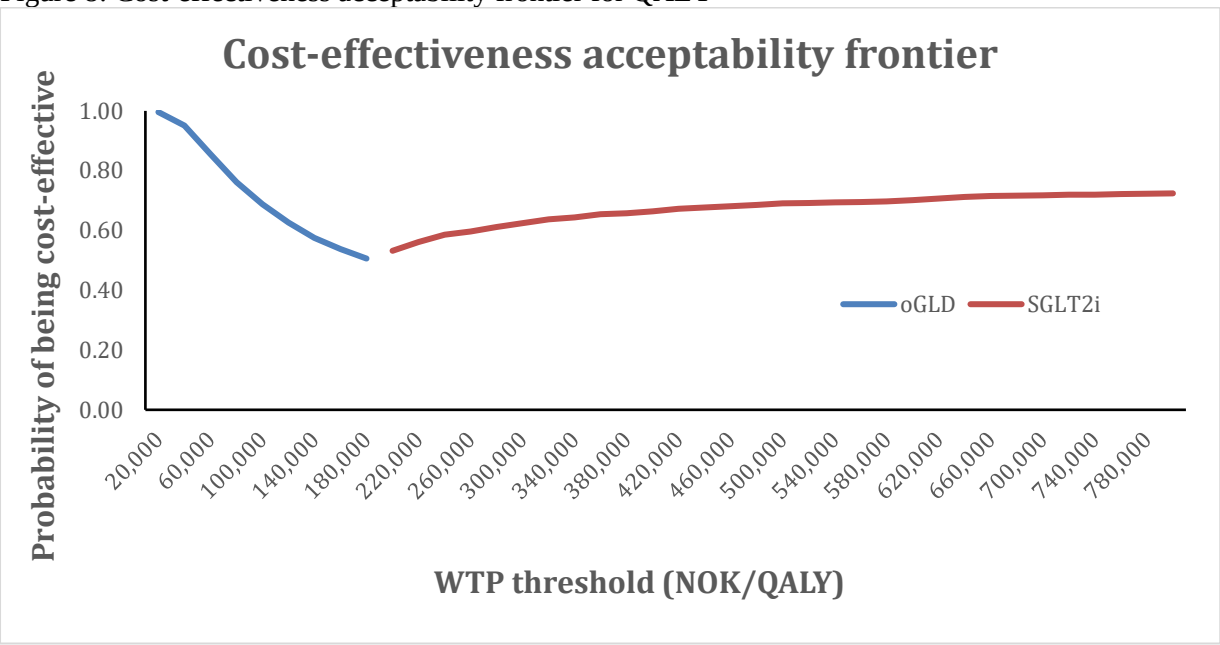


Figure 8: Cost-effectiveness acceptability frontier for QALY



Life Years

Figure 9 shows the probability of oGLD and SGLT2 inhibitors being cost-effective, given different values of the WTP threshold for life years. The standard treatment, oGLD, is the most cost-effective treatment for WTP threshold-values up to NOK 124,125. For values above this the intervention is most cost-effective. The probability of being cost-effective flattens out at

approximately 75%. Figure 10 shows only the cost-effective option for all WTP threshold values.

Figure 9: Cost-effectiveness acceptability curve for Life years

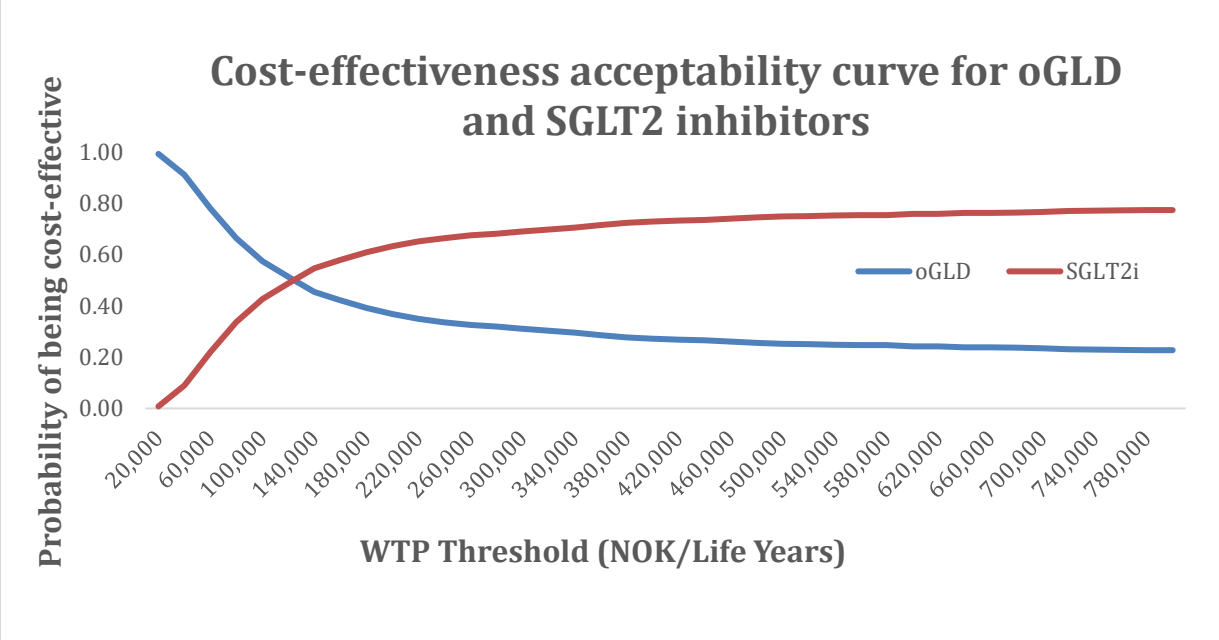
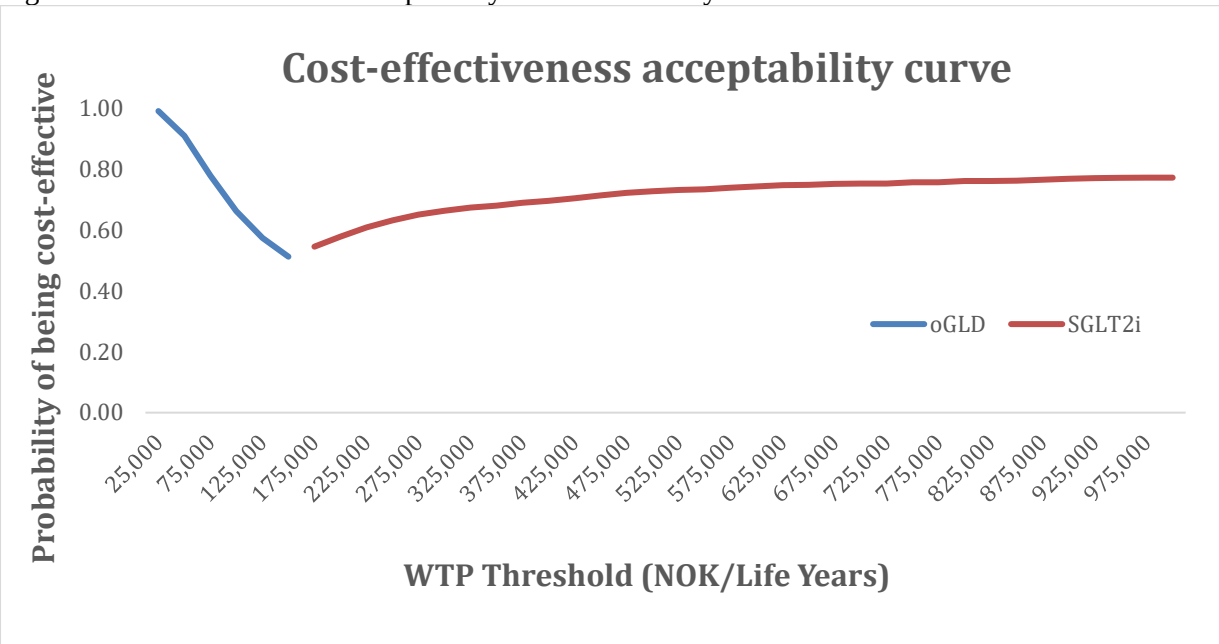


Figure 10: Cost-effectiveness acceptability frontier for Life years



6 Discussion

The results with the deterministic values indicate that the SGLT2 inhibitors are cost-effective compared to the standard treatment in Norway. The PSA estimated that the SGLT2 inhibitors are more cost-effective compared to the standard treatment at WTP thresholds above NOK 174,050 for QALYs and NOK 124,125 for LYs.

6.1 Strengths and limitations

6.1.1 Health outcomes

In this CUA, both QALYs and LY gained are used as health outcomes. The expected health effects include mortality and morbidity. When including both measures, it is possible to look at the change in mortality, in addition to the change in the quality of life. As Figure 7 and 9 shows, the SGLT2 inhibitors treatment are cost-effective at a WTP threshold of NOK 174,050 (QALYs) and NOK 124,125 (LYs) compared to standard of care. By comparing the two health effects, it is possible to assume that the intervention makes people live longer compared to the standard of care, in addition to give higher quality of life.

The utility values used in this thesis are found in a paper from the United Kingdom. The utility value of having T2DM in the United Kingdom is estimated to be 0.785 (Clarke et al., 2002), while in Norway it is estimated to be 0.850 (Solli et al., 2010). As the tornado plot presented in Figure 4 shows, the utility value of having T2DM are the 4th most sensitive variable on the iNMB. By using the Norwegian values from Solli et al. for the health states T2DM, myocardial infarction (both 1st year and the following years) and stroke (both 1st year and the following years), the new discounted incremental QALY equals 0.33. This is an increase of 0.03 QALYs compared to the result using values from the United Kingdom, giving a lower ICER indicating that the intervention would have been even more cost-effective using Norwegian values.

Utility may have values below zero, and consequently one could use 1-gamma for the probabilistic values, as suggested by Briggs et al. (2006). Since we are simulating the mean, and none of the mean values indicates negative utility values, it is most appropriate to use the distribution that cannot take negative values. That is the reason why beta-distribution is chosen.

There are some disagreements when it comes to which utility measurement to use. Speight, Reaney, and Barnard (2009) claim that the EQ-5D measures quality of health and not quality of life, and that the EQ-5D lack responsiveness for use in diabetes. The NICE methodology guidance on the other hand, writes that the preferred measure of health-related quality of life in adults, is EQ-5D (National Institute for Health and Care Excellence, 2013). Even though the descriptive systems of the EQ-5D is limited, it captures the impact of diabetes complications with both respect to EQ-5D index and each of the dimensions (Solli et al., 2010). Consequently, individual EQ-5D dimensions seems suited to capture most diabetes-related events.

Since this thesis includes some simplifications, it might be some events excluded that could have affected the utility values, if they were included. For instance, a person's inner fear living with low blood sugar does not necessarily impact any of the variables in the EQ-5D questionnaire, like pain or mobility. Rather, it might affect aspects of more general quality of life, like spontaneity, ability to work and enjoyment of leisure activities.

6.1.2 Costs

In this thesis, there are a mix of costs from Norway and from the United Kingdom. All the costs of drugs, costs of having myocardial infarction and stroke the first year after the event are found in a Norwegian setting, presented in NOK. The costs of having amputation, both the first year and the following years, and the costs of having myocardial infarction and stroke the after the first year, are obtained from the United Kingdom and converted into NOK. The preferred option would be to have all costs obtained from Norway, as the price-levels are different from country to country. E.g. Malawi has a low threshold value, due to being the country with the lowest per capita income in the world (Woods, Revill, Sculpher, & Claxton, 2016). Converting costs from this country to NOK would probably create a huge bias. However, the differences between Norway and the United Kingdom is not that big. In addition, the tornado plot presented in Figure 4 shows that a change in any of the costs will have a small impact on the iNMB, though the Tornado plot may not include all uncertainty.

Some of the cost parameters lacked the confidence interval needed to estimate the standard error. To correct for this the upper confidence level is assumed to be 20% higher than the deterministic value. As a consequence of my assumption, the estimated standard error can be too high which will give a greater spread of the observations in the PSA.

6.1.3 Mortality

The increased risk of dying from T2DM compared to people without T2DM is in this thesis is assumed to be 1.588 and was estimated from mortality rates found in an article from the United Kingdom. As this thesis has a Norwegian perspective, it would be better if the estimation was based on mortality rates from Norway. However, the increased risk is multiplied with probabilities for dying for ages 60 to 100 found in a Norwegian setting.

The probability of dying from myocardial infarction and stroke within the first year after the event, is found by dividing the number of patients who died from the disease in 2016, on the number of people who got the disease the same year. This estimate is quite uncertain, as it is realistic to assume that some of the patients who died from myocardial infarction or stroke in 2016 have had the diagnose for more than one year. The estimates would be more precise if data about patients with T2DM dying within one year after being diagnosed with myocardial infarction or stroke had been available. As this thesis have a Norwegian health care perspective, such data would yield even more precise estimates if gathered from a Norwegian study.

The probability of dying from myocardial infarction and stroke after the first year of the event, is found by estimating the increased risk of dying compared to a person without the disease. This is found in an article written by Majed et al. (2015). To estimate the increased risk of dying, numbers from patients with no previous CVD is used. The tornado diagram presented in Figure 4 confirms that a change in these two parameters have a small effect on the iNMB, and that using patients with previous CVD to estimate the increased risk of dying are therefore likely to have small effect on the result. However, the Tornado plot may not include all uncertainty.

6.1.4 Intervention

According to Drummond et al. (2015), all relevant alternatives which might have an impact of the result should be included in the study. In this thesis, including more than just one of the glucose-lowering drugs-group is therefore recommended, but due to the time frame of this thesis, only the SGLT2 inhibitors-group are included.

6.1.5 Markov model

Health states

In the Markov model, there are three diabetes-related complications included: myocardial infarction, stroke and amputation. There are more diabetes-related complications that could have been included in the model, such as kidney failure, blindness, foot disease and hospitalization for heart failure. Myocardial infarction and stroke are included in the model, as that they are the most common macrovascular complications for patients with T2DM. Amputations is also interesting to include, as the meta-analysis by Zelniker et al. showed that the SGLT2 inhibitors had a negative effect on amputations, while the SGLT2 inhibitors had a positive effect on myocardial infarction, and almost no effect on stroke. In addition, amputation had with the greatest disutility value compared to the other events included.

Key assumptions

Of course, the Markov model is a simplification of reality. In the model in this thesis, it is not possible to move between myocardial infarction and stroke, myocardial infarction and amputation or stroke and amputation. In addition, a patient with T2DM might, in the real world, experience myocardial infarction, stroke or amputations more than once. This is not possible in this model. In addition, the model only allows for staying in one cycle at a time, while in the real world a person may experience e.g. both stroke and amputation within the same year.

The incidence values used in this thesis are calculated separately. As an example, the incidence of myocardial infarction is calculated without taking into account the incidence of stroke, and vice versa. The numbers for first-time stroke and first-time myocardial infarction will be correct separately. As a consequence, the model does not answer whether a person who gets both stroke and myocardial infarction would have higher or lower cost or QALY, compared to two persons, one person with a stroke and one person with myocardial infarction.

Another assumption made is that there is no difference between the outcomes after myocardial infarction, stroke or amputation. In the real world a person having a stroke can regain its old function or end up in a wheelchair in a nursing home. A more precise estimate should therefore be looking at different outcomes from each health state and estimate costs and health effects for each state. This would probably have an impact on the results.

Amputations

In this thesis, I have developed a random-effect meta-analysis of amputation with data from three different clinical trials. The trials showed that the incidence of amputations was highest in the CANVAS program (Canagliflozin), compared to the EMPA-REG (Empagliflozin) and DECLARE (Dapagliflozin) programs. A possible explanation of why the CANVAS program showed highest incidence of amputations, might be that the incidence of amputations in the placebo-group in the CANVAS program was low compared to the placebo-group in the other programs. A study published in April this year, looking into Canagliflozin and Renal outcomes in T2DM and nephropathy (Perkovic et al., 2019), found that there were no significant differences in rates of amputation between Canagliflozin and the placebo-group. If that is the case, and not an actual increased risk for amputations due to active treatment with canagliflozin, SGLT2 inhibitors would have been even more cost-effective. Hence, the conclusion would still be the same.

The systematic review by Thorud et al. (2016), which was used in the calculation of mortality after amputation, did not differ between Type 1 Diabetes Mellitus, and Type 2 Diabetes Mellitus when looking at the mortality rate after amputation. If there is a difference between the mortality rate after amputation for the different types of diabetes, this could affect the results.

Hazard ratios

The hazard ratios in this thesis are the estimate of the effect of SGLT2 inhibitors, and it is common that the estimates of effect have a large impact on the result. As shown in the deterministic sensitivity analysis, and the tornado plot presented in Figure 4, the values of hazard ratios for all-cause mortality, stroke and myocardial infarction are the parameters which are most sensitive to changes and its impact on the iNMB. The value of hazard ratio for amputation is the 5^{th} most sensitive parameter. However, Figure 4 also shows that none of the parameters have iNMB values below 0, meaning that the conclusion still is the same. All the hazard ratios used in this thesis are obtained from one meta-analysis, written by Zelniker et al., and they are the drivers of the cost-effectiveness results. Using values from other sources could have an impact on the result, as a small change in these parameters will have a large impact on the iNMB.

6.1.6 Half-cycle correction

As mentioned in section 4, half-cycle correction has been used in this thesis, by calculating the mean of the previous and the present year. However, there is no consensus on why and how to perform the correction. Though some argue that half-cycle correction gives a more precise reflection of reality than not applying it, some argue that other methods can reduce the risk of errors even further. A paper written by Elbasha and Chhatwal (2016) presents different within-cycle correction methods. They found situations where a wrong decision can be made if the more accurate method is not applied. When the ICER is near a WTP threshold, the choice of method may determine whether an intervention is cost-effective (Elbasha & Chhatwal, 2016).

In Norway, there are no clear guidelines on why and how to do half-cycle correction. Though, in a note written to NoMA "Input to Guidelines for submission of documentation for single technology assessment (STA) of pharmaceuticals", it is proposed that the guidelines should include a preparation of when half-cycle correction should be used and when such adjustment is not necessary (Aas, 2017).

6.1.7 Discount rate

The discount rate used also have some impact on the result in this analysis. Having T2DM and being in all health states except from death, do have costs associated with it. The consequence of preventing for example a stroke 5 years ahead of time, results in 82.8% of the same health benefit as preventing a case of stroke today, when using a discount rate of 4% (1.04^{-5}).

The choice of discount rate is much discussed and varies among nations. While the discount rate in Norway, recommended by NoMA and the Norwegian Ministry of Finance, is 4%, other countries such as the United Kingdom operates with a common discount rate at 3.5%. The United Kingdom has also introduced selective discount rates which means that the discount rate can vary for costs and effects. In some cases where the health gains last for 30 years or more, a discount rate at 1.5% is used in health gains, while the discount rate in costs is 3.5% (Paulden, O'Mahony, Culyer, & McCabe, 2014). This may lead to inconsistencies and strategic behavior to ensure more favorable cost-effectiveness ratios for specific drugs or treatments.

When the discount rate is set to a constant 4%, as in this thesis, the intervention with immediate health gain will be prioritized before interventions who seek to prevent diseases in the future.

Thus, how discount rate used in health studies will impact the calculated cost-effectiveness for different interventions.

6.1.8 Future studies

As this thesis is a cost-utility analysis, an additional analysis would be of high interest for further studies; a value of information analysis (VOI). The reason is that the VOI analysis is regarded as a valuable extension of probabilistic cost-effectiveness analysis, as it provides information about the consequences of adopting the wrong treatment strategy (Briggs et al., 2006). VOI informs the decision makers about the expected costs of uncertainty, and the value of information to reduce the uncertainty (Oostenbrink, Al, Oppe, & Rutten-Van Mölken, 2008). The two most used VOIs are the expected value of perfect information (EVPI) and the expected value of partially perfect information (EVPPI). EVPI is the price that a healthcare decision-maker would, in theory, be willing to pay to have perfect information regarding all factors that influence which treatment choice is preferred as the result of a CEA (York Health Economics Consortium, 2016b). This is the value, in monetary terms, of removing all uncertainty. EVPPI on the other hand, is the price that a healthcare decision-maker would, in theory, be willing to pay in order to gain perfect information for one or more factors (York Health Economics Consortium, 2016a). When including all parameters in the EVPPI, one can find which contribute most to the overall decision uncertainty. Both the EVPI and the EVPPI are valuable, as the decision-maker does not only have to decide on treatment strategy, but also whether more research regarding the decision is needed (Oostenbrink et al., 2008).

A study published in April this year, found that among patients with T2DM and kidney disease, the patients in the Canagliflozin group had lower risk of kidney failure, cardiovascular death, myocardial infarction and stroke compared to the patients in the placebo group (Perkovic et al., 2019). A cost-effectiveness study looking into the use of Canagliflozin for patients with kidney failure could therefore be of high interest.

As this study is based on one observational study and one meta-analysis for finding the effects of SGLT2, it would be interesting for future studies to use other observational studies and meta-analysis to compare the effect. Future studies should also focus on finding inputs from a Norwegian setting, for improving the input-parameters.

7 Conclusion

The Markov model developed is adapted to the Norwegian health care perspective and estimates that the incremental cost of adding SGLT2 inhibitors to oGLD is NOK 49,617. The incremental effect of SGLT2 inhibitors is 0.30 QALYs, and 0.42 LYs gained, giving the incremental cost-effectiveness ratios of NOK 166,000 per QALY and 117,000 per LY. Given the assumed threshold of NOK 475,000 per QALY and LY gained, simulations indicate a 68.3% probability that SGLT2 inhibitors are cost-effective for QALYs, and a 74.3% probability that SGLT2 inhibitors are cost-effective for LYs.

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Appendix

Table 10: Probability of dying from different health states given age, using oGLD and SGLT2 inhibitors

	Other glucose lowering drug				SGLT2 inhibitors			
Age	**T2DM**	**Post Myocard. Inf.**	**Post Stroke**	**Post Amputation**	**T2DM**	**Post Myocard. Inf.**	**Post Stroke**	**Post Amputation**
60	0.008	0.020	0.032	0.129	0.007	0.017	0.027	0.099
61	0.008	0.021	0.033	0.123	0.007	0.018	0.028	0.097
62	0.009	0.023	0.037	0.118	0.008	0.020	0.031	0.095
63	0.011	0.028	0.044	0.113	0.010	0.024	0.038	0.094
64	0.011	0.028	0.045	0.107	0.010	0.024	0.038	0.091
65	0.013	0.032	0.051	0.102	0.011	0.027	0.044	0.089
66	0.015	0.038	0.060	0.098	0.013	0.033	0.052	0.087
67	0.017	0.041	0.065	0.093	0.014	0.035	0.056	0.084
68	0.018	0.045	0.071	0.088	0.016	0.039	0.061	0.081
69	0.020	0.050	0.079	0.084	0.017	0.043	0.067	0.078
70	0.022	0.053	0.084	0.079	0.018	0.045	0.072	0.075
71	0.024	0.059	0.093	0.076	0.020	0.051	0.080	0.073
72	0.028	0.067	0.106	0.074	0.023	0.058	0.091	0.071
73	0.031	0.076	0.118	0.073	0.026	0.065	0.101	0.070
74	0.033	0.079	0.124	0.070	0.028	0.068	0.106	0.067
75	0.037	0.091	0.142	0.070	0.032	0.078	0.122	0.067
76	0.039	0.094	0.147	0.068	0.033	0.081	0.126	0.065
77	0.046	0.111	0.171	0.071	0.039	0.095	0.147	0.067
78	0.054	0.130	0.200	0.076	0.046	0.112	0.173	0.070
79	0.058	0.138	0.212	0.076	0.049	0.119	0.183	0.070
80	0.068	0.161	0.246	0.084	0.058	0.139	0.213	0.076
81	0.078	0.184	0.278	0.092	0.067	0.159	0.242	0.083
82	0.082	0.192	0.290	0.094	0.070	0.166	0.252	0.084
83	0.091	0.212	0.316	0.101	0.078	0.183	0.276	0.089
84	0.110	0.253	0.373	0.119	0.094	0.219	0.328	0.104
85	0.121	0.277	0.405	0.129	0.104	0.241	0.357	0.113
86	0.142	0.318	0.459	0.148	0.122	0.278	0.406	0.130
87	0.157	0.347	0.495	0.163	0.135	0.304	0.441	0.141
88	0.171	0.374	0.528	0.176	0.147	0.329	0.472	0.153
89	0.204	0.435	0.599	0.208	0.176	0.384	0.540	0.181
90	0.227	0.474	0.643	0.231	0.196	0.421	0.583	0.201
91	0.245	0.506	0.677	0.249	0.213	0.451	0.617	0.217
92	0.275	0.553	0.724	0.279	0.239	0.495	0.666	0.243
93	0.295	0.583	0.754	0.299	0.257	0.525	0.696	0.261
94	0.333	0.638	0.803	0.337	0.292	0.578	0.749	0.295
95	0.384	0.702	0.856	0.387	0.337	0.643	0.808	0.341
96	0.396	0.718	0.868	0.400	0.349	0.659	0.821	0.352
97	0.413	0.736	0.882	0.417	0.364	0.678	0.837	0.368
98	0.436	0.762	0.900	0.442	0.386	0.705	0.858	0.390
99	0.465	0.791	0.919	0.471	0.412	0.736	0.881	0.417
100	0.494	0.818	0.935	0.502	0.440	0.765	0.902	0.445