Health Technology Assessment (HTA) of GLP-1 receptor agonists and SGLT-2 inhibitors in combination with metformin as first-line treatment in patient with type 2 diabetes mellitus (T2DM) and established cardiovascular or chronic kidney disease

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Abstract

Type 2 diabetes mellitus (T2DM) is one of the most prevalent lifestyle-related diseases, causing increased mortality, morbidity and reduction in health-related quality of life (HRQoL), as well as costs to society related to treatment, follow-up and production losses.In the current guidelines, SGLT-2 inhibitors and GLP-1 analogs are recommended as second-line treatment for T2DM. Based on results from recent studies, we have in this report analyzed whether these drugs can be considered cost-effective as first-line treatment (in combination with metformin) for patients with T2DM with either established cardiovascular disease or chronic renal failure (only SGLT-2 inhibitors considered). Based on two decision analytic models we estimated the incremental cost per QALYs gained. For the patients with T2DM and established CVD, SGLT-2 i is the preferred alternative (ICER NOK 59,811 per LY gained and NOK 89,517 per QALY gained) and is superior to GLP-1 RA, as SGLT-2 I resulted in higher health outcomes than GLP-1 RA. For patients with T2DM and established renal failure when comparing SGLT-2 i to metformin results in an ICER of NOK 168,872 per LY gained and NOK 193,656 per QALY gained. Both ICERs fall below the the threshold for these two patient groups are NOK 475,000.

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List of Abbreviations

AE:	Adverse event
AKI:	Acute kidney injury
BIA:	Budget impact analysis
CBA:	Cost-benefit analysis
CEA:	Cost-effectiveness analysis
CEAC:	Cost-effectiveness acceptability curve
CUA:	Cost-utility analysis
CKD	Chronic Kidney Disease
CVD	Cardiovascular disease
ESKD	End-stage kidney disease
EVPPI:	Expected value of partially perfect information
EVPI:	Expected value of perfect information
HF	Heart failure
HRQoL:	Health-related quality of life
HTA	Health Technology Assessment
ICER:	Incremental cost-effectiveness ratio
MI	Myocardial infarction
NIPH	National Institute of Public Health
NMB:	Net monetary benefit
NOMA	Norwegian Medicines Agency
PICO	Population, intervention, comparator and outcome
PSA:	Probabilistic Sensitivity Analysis
QALY:	Quality-adjusted life-year
RCT:	Randomized controlled trial
T2DM:	Type 2 diabetes mellitus
VOI:	Value of information (analysis)
WTP:	Willingness-to-pay

Contents

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent lifestyle related diseases, causing increased mortality, morbidity and reduction in health-related quality of life (HRQoL) for the patients and costs for society related to treatment, follow-up and production loss (Ruiz et al 2018).

Treatment of T2DM consists mainly of glucose lowering therapy and cardiovascular prophylaxis. Glucose lowering therapy is traditionally based on lifestyle interventions, and on glucose-lowering medication to control glucose and the Haemaglobin A1c (HbA1c) level. Metformin has been recommended as first line treatment as best Standard of Care (SoC). If treatment with metformin is not sufficient to reduce symptoms and reach HbA1c targets, other glucose-lowering drugs are added. In Norway, drugs belonging to the following classes are available: Dipeptidyl peptidase – 4 (DPP-4) inhibitors, glucagon-like peptide 1 receptor agonist (GLP-1 RA), sodium-glucose co-transporter 2 inhibitors (SGLT-2i), sulphonylureas (SU), glitazones/thiazolidinedone (TZD), acabose and insulin. Recently, evidence from new trials of SGLT-2 inhibitors and GLP-1 RAs indicate that such drugs may have beneficial effects on cardiovascular and kidney outcomes independent of or beyond their glucose lowering effects.

The present 2019-revision of the Norwegian treatment guidelines, recommends that SGLT-2is and GLP-1 RAs be considered added as second line agents in patients with cardiovascular or renal diseases that do not reach their target of HbA1c with lifestyle measures and metformin alone.

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC), in collaboration with the European Association for the Study of Diabetes (EASD), published the "2019 ESC Guideline on diabetes, pre-diabetes, and cardiovascular disease developed in collaboration with the EASD" in august 2019. This was the third version of their guideline for the management and prevention of cardiovascular disease (CVD) in subjects with and in risk of developing T2DM (ref). The guideline recommends an SGLT-2 inhibitor or GLP-1 RA with proven CVD benefit in monotherapy to drug naïve patients if established atherosclerotic CVD and in patients with high/very high CV risk. For patients already on metformin with the same risk profile, it was recommended to add either drug. These recommendations were given independent of HbA1c level.

The clinical guideline "Management of Hyperglycemia in Type 2 Diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the study of diabetes (EASD)" recommended to add an SGLT-2 inhibitor or GLP-1 RA with proven CVD benefit if HbA1c target not was reached on metformin, and the patient had established atherosclerotic CVD or chronic kidney disease (CKD). If heart failure (HF) or CKD predominated, an SGLT-2 inhibitor with evidence

of reducing HF and/or CKD progression was preferred. These recommendations were revised in a 2019 update (Buse et al Diabetes Care 2020). In this update it was recommended to consider, independent of HbA1c level, to add an SGLT-2 inhibitor or a GLP-1 RA to metformin, in patients with "indicators of high risk or established atherosclerotic CVD, or with CKD or HF".

The recommendations from the ESC and the ADA/EASD consensus report differ slightly, the main difference being that ESC recommends SGLT-2 inhibitor or GLP-1 RA in monotherapy as first line treatment to some patients. However, both these guidelines differ from the current national diabetes guideline in Norway where treatment with the new drugs depends on inadequate HbA1c levels with metformin.

As it has been established that several drugs among the SGLT-2 inhibitors and GLP-1 RAs may provide organ protection, independent of HbA1c levels, a revision of the Norwegian guideline was deemed necessary, and in order to provide evidence on both efficacy and cost-effectiveness, an HTA was needed.

It was decided that the HTA should assess efficacy and cost/benefit for the two settings with currently sufficient patient data for the analyses that would need to be conducted, and with the highest likelihood of cost-effectiveness, i.e. to recommend SLGT-2 inhibitors or GLP-1 RAs as **first line treatment together with metformin** to patients with established CVD or CKD.

It was the opinion of Helsedirektoratet that data on SGLT-2 inhibitors and GLP-1 RAs as first line treatment in monotherapy, and treatment in the primary prevention setting, currently not was available in quantities that would make health economic evaluations feasible. It was therefore decided to start with the two patient groups and settings described above.

The evidence for the efficacy of SGLT-2 inhibitors and GLP-1 RAs are mainly based on clinical trials where these drugs or placebo were given as add-on therapy to best standard of care (SoC), most often added to metformin in combination with other glucose lowering drugs, in situations where best SoC not reduced HbA1c levels sufficiently (Palmer et al 2021, Li et al 2021). The comparator in this HTA is thus "best SoC".

2. Background

2.1 Type 2 Diabetes and treatment options

2.1.1 Epidemiology

Diabetes is one of the most common chronic disorders in Norway (NIPH, 2017). Type 2 diabetes mellitus (T2DM) is the most prevalent type of diabetes and accounts for around 90% of all cases

(Goyal and Jialal, 2020). The Norwegian Norhealth registry reported 42 users of drugs for type 2 diabetes per 1000 inhabitants aged 30 to 74 years in 2020. Gender wise, more men than women have diabetes in Norway, being approximately eight women per ten men (Strøm, 2014). There is an increase in both prevalence and incidence of T2DM with age, reaching a peak at about 80 years (NIPH, 2017).

2.1.2. Pathophysiology

T2DM is a chronic metabolic disorder characterized by a persistent high level of glucose in the blood stream (i.e., hyperglycaemia). T2DM is caused by a combination of impaired insulin secretion by the pancreas and insulin resistance (i.e., diminished response to insulin) (NIPH, 2017). Initially, the ineffectiveness of insulin is countered by an effort of the pancreas to increase insulin production and maintain glucose homeostasis. However, insulin production decreases over time, resulting in T2DM.

There are various risk factors involved in the development of insulin resistance and eventually T2DM. A vast majority of diabetic patients are obese and have a high body fat percentage which further promotes insulin resistance through various inflammatory mechanisms. According to Midthjell (2001), patients with a body mass index (BMI) of 30 kg/m^2 have more than 20 times higher risk of developing T2DM over an 11- year period compared with patients with a BMI of 22 kg/m^2 (i.e., normal weight). The presence of dyslipidaemia (i.e., abnormal high levels of fat in the blood stream), lack of physical activity, unhealthy diet, smoking, family history of diabetes, and previous gestational diabetes are factors that also increase the risk of developing T2DM (NIPH, 2017).

2.1.3. Presentation and Symptoms

Patients with T2DM usually present with 3 main symptoms 1) increase urination, 2) increased thirst and 3) increased appetite. However, symptoms like fatigue or energy loss, bacterial and fungal infections, and delayed wound healing, are frequent presentations of T2DM. Some patients have also reported numbness in hands or feet and blurred vision as main symptoms (Goyal and Jialal, 2020). Furthermore, patients with diabetes have a substantially increased risk for cardiovasular and neurovascular complications, and it is not uncommon that patients with T2DM suffer from these or other complications before being diagnosed with diabetes.

2.1.4 Complications and Comorbidities

T2DM complications are the result of a sustained hyperglycaemia often without adequate control and it can affect many major organs like heart, kidneys, eyes, blood vessels and nerves. Often complications also increase the risk for other serious chronic diseases like kidney disease, dementia and Alzheimer's disease, cataract, glaucoma, and hearing impairment (Directorate of Health, 2016). Potential complications of diabetes include:

- CVD: ischemic heart disease (angina, myocardial infarction), stroke and heart failure
- Peripheral neuropathy: gradual damage of nerves in limbs that results in numbness, burning pain, or eventual loss of feeling.
- Autonomic neuropathy: nerve damage may occur in the conduction system of the heart and lead to irregular heart rhythms, it can cause dysfunction in blood pressure regulation and bladder emptying. Damage in the digestive system may cause vomiting, nausea, constipation, or diarrhoea. Nerve damage can also contribute to erectile dysfunction in men.
- Chronic kidney disease
- Skin or mucosal infections: due to susceptibility of bacterial or fungal infections due to increased tissue glucose and an impaired immune system
- Delayed wound healing, sometimes combined with infections. Poorly controlled lesions sometimes end with amputation.
- Eyes: retinopathy and blindness

2.1.5. Diagnosis

The diabetes diagnose should preferably be made by measuring the level of glycated haemoglobin (HbA1c). It may also be diagnosed based on the concentration of plasma glucose. The latter can be measured by a random plasma glucose, a fasting plasma glucose (FPG) test or a two- hour oral glucose tolerance test (OGTT). A value that meets the diagnostic criteria must be confirmed in a new sample, unless a random sample is above 11.1 mmol/L and accompanied by diabetes symptoms.

2.1.5.1. Glycated Haemoglobin A1C

Patients with HbA1c greater than 48 mmol/mol (6.5%) are diagnosed with diabetes mellitus. HbA1c gives an average of blood glucose over the last 2 to 3 months which makes it less prone to the variation due to pre-analytical variables and biological variation (Directorate of Health, 2016).

2.1.5.2. Fasting Plasma Glucose

A blood sample is taken after an 8 hour overnight fast. According to Norwegian diabetes guideline (Directorate of Health, 2021), a FPG level of more than 7.0 mm/L (126 mg/dl) confirms the diagnosis of T2DM.

2.1.5.3. Two-Hour Oral Glucose Tolerance Test

The plasma glucose level is measured before and 2 hours after the ingestion of 75 mg oral glucose. The diagnosis is confirmed if the plasma glucose level after 2 hours is more than 11.1 mmol/L (200 mg/dl) (Directorate of Health, 2016).

2.1.6. Treatment

Diet and exercise are the cornerstones of diabetes prevention and treatment. Patients should be encouraged on an exercise routine with a duration of minimum 150 minutes per week and a diet low in saturated fat and high in fiber and monounsaturated fat (Directorate of Health, 2016), Eckstein et al., 2019).

According to the current Norwegian national diabetes guideline, if adequate glycemia cannot be achieved after diet and exercise, metformin is the first-line therapy given as 850 mg per daily dose. Following metformin, other glucose-lowering drugs can be prescribed such as glucagon-like-peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transorter-2 (SGLT-2) inhibitors, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, pioglitazone, or insulin.

Recent meta-analyses (Li et al., 2021; Palmer et al., 2020; Tsapas et al., 2020) have shown that GLP-1 receptor agonists and SGLT-2 inhibitors reduce CV disease, mortality and the risk of developing end-stage kidney disease (ESKD) in patients at high CV and renal risk. Both GLP-1 receptor agonists and SGLT-2 inhibitors reduce these risks regardless of the initial plasma glucose level of the patient, but this has not been extensively tested in patients with HbA1c below 53 mmol/mol and even less in patients with HbA1c below 48 mmol/mol (Buse et al., 2020).

2.1.6.1 Glucagon-like peptide-1 receptor agonist

GLP-1 RAs have proven to have beneficial effects on CV and kidney outcomes as well as CV mortality (Li et al., 2021; Palmer et al., 2020; Tsapas et al., 2020; Kristensen et al., 2019). They work by mimicking the functions of the hormones in the body that help control post-meal blood sugar

levels, maintain body weight and have a modest effect on blood pressure. Furthermore, GLP-1 receptor agonists can decrease the apoptosis process of the cells responsible for insulin secretion while also promoting their proliferation (Collins & Costello, 2021). Some of the side effects associated with GLP-1 are gastrointestinal events, such as nausea, diarrhea, vomiting, indigestion, appetite loss, and constipation. The administration of GLP-1 receptor agonists can vary depending on the specific drug, ranging from once-daily doses (for lixisenatide and liraglutide), once weekly (for albiglutide, dulaglutide, and semaglutide), and twice daily (for exenatide) (Collins & Costello, 2020).

2.1.6.2 Sodium-glucose co-transorter-2 inhibitors

SGLT-2 inhibitors exert much of their protective effects against heart failure (HF), renal disease and CV mortality (Li et al., 2021; Palmer et al., 2020; Tsapas et al., 2020; Kristensen et al., 2020). The mechanism of action of SGLT-2 consists of inducing the loss of sodium and glucose in the urine. Therefore, their most common side effects are genitourinary infections. Other side effects are dehydration, diabetic ketoacidosis, acute kidney injury (AKI), bone fractures, amputation, and gangrene. All SGLT-2 inhibitors are administered once daily.

2.2 Economic Evaluation

Economic evaluation is a comparative analysis measuring and weighing the costs and consequences of two or more courses of action at a given point in time (Drummond et al, 2015). In the field of health care, these analyses are done for the purposes of informing decisions about for instance reimbursement of new treatments. In this analysis both cost-effectiveness analyses (CEA) and cost-utility analyses (CUA) are being applied (Drummond et al, 2015). The only difference between the two analyses, are how health outcomes are measured. In this analysis, life years are used as health outcome in the CEA, while quality-adjusted life-years (QALY) are used in the CUA, where the latter is the main analysis.

To understand CUA, the concept of QALYs must be explained. QALYs are a generic health measure, which measure the years lived in good health. Therefore, the measure can simultaneously account for gains in both longevity and quality of life. It is computed by multiplying the years lived in a given health state with a value representing the health-related quality of life (HRQoL):

$$QALY = HRQoL\ x\ years\ in\ health\ state$$

HRQoL is a utility value representing the quality of life in a specific health state. This utility value typically ranges from 0 (death) to 1 (perfect health) and describes the disease burden associated with a certain health state (Drummond et al, 2015).

The incremental cost-effectiveness ratio (ICER) is a commonly reported outcome of a CUA. The ICER represents the incremental costs per incremental health gained when comparing one treatment with another. In a CUA, the ICER is defined by

$$ICER = \frac{Cost\ of\ new\ treatment - Cost\ of\ standard\ of\ care}{QALYs\ of\ new\ treatment - QALYs\ of\ standard\ of\ care}$$

The ICER is often compared with a cost-effectiveness threshold, which represents the willingness-to-pay (WTP) for an incremental gain in health benefit. In Norway the WTP is weighted with severity. Another way of expressing the ICER is by the incremental net monetary benefits (NMB), defined by

$$NMB = Threshold \times Incr\ Effect - Incr.Cost$$

Sensitivity analyses are a way to assess uncertainty in a model. Parameter uncertainty refers to uncertainty in the inputs of the parameters in the model (e.g. cost and effectiveness parameters). Sensitivity analyses can be deterministic or probabilistic. A deterministic analysis is generally not sufficient to address uncertainty, as it represents events that are extreme and highly unlikely. A probabilistic sensitivity analysis (PSA) samples each uncertain parameter with an appropriate distribution and records the result with each set of parameters. This is repeated multiple times (e.g. 10 000) to achieve a likely range and distribution of outcomes (Drummond et al, 2015). A probabilistic analysis can be presented in the form of a cost-effectiveness acceptability curve or as a scatterplot on the cost-effectiveness plane (CE-plane). The x-axis on a CE-plane represents the incremental effect (QALYs) of the intervention (i.e. the denominator of an ICER) and the y-axis represents incremental costs (i.e. the numerator of an ICER). A straight line is drawn through the origin, which represents the WTP-threshold. The simulated ICERs from a PSA are plotted on the

plane, and all the estimates falling below the threshold-line are considered cost-effective with regards to the particular threshold (Drummond et al, 2015). Figure 1 illustrates:

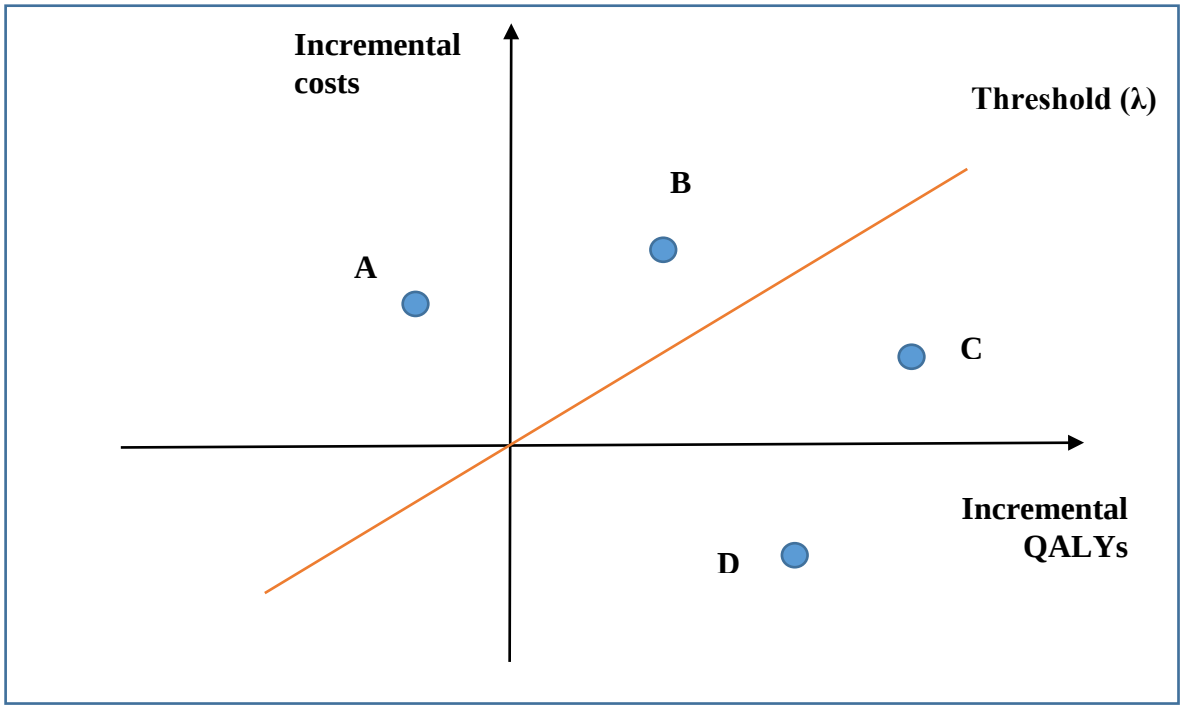

Figure 1: Cost-Effectiveness Plane. λ represents the threshold, with four (A, B, C and D) alternative.

The CE-scatterplot gives an indication of the uncertainty associated with the ICER (spread), as well as whether that uncertainty is driven by costs or effects.

A cost-effectiveness acceptability curve (CEAC) plots the probability of a treatment being cost-effective as compared to the other treatment lines under consideration (according to a PSA) against a range of cost-effectiveness thresholds. This enables a straightforward inspection of the effect of uncertainty on the probability of making a treatment recommendation that is (not) cost-efficient. The probability represents the proportion of simulations where a given treatment has the highest net benefit in relation to the comparators (Drummond et al, 2015). A CEAC can provide an easy-to-interpret visualization of cost-effectiveness. However, in some cases the treatment with the highest probability to be cost-effective may not be the treatment with the highest expected net benefit (Drummond et al, 2015).

3. Clinical efficacy and adverse events

A literature search was carried out in the PUBMED database to investigate the clinical effectiveness and safety of SGLT-2 inhibitors and GLP-1 RAs on diabetic patients with CV and renal disease. The search initially focused on the effect of the best standard of care (i.e., metformin) for these patient populations. Once this baseline effect was investigated, the search focused specifically on the effect of both SGLT-2 inhibitors and GLP-1 RAs in diabetic patients with CV and renal disease. Clinical trials, cohort studies and meta-analyses were the main type of studies from which evidence was taken.

3.1 Inclusion criteria

The inclusion criteria are presented in Table 1 according to PICO.

Table 1: PICO, inclusion criteria

	Definition	Explanation
Population	Individuals with short-term diagnosed T2DM, - Cohort 1: with either established cardiovascular disease - Cohort 2: with chronic kidney disease with or without heart failure	CVD (myocardio infarction, angina, and stroke, both hemorrhagic, ischemic and TIA) includes ICD-10 codes: I21-I22, I25.2, I25.6, I20.0, I20.1, I20.8, I20.9, I25.1, I25.5, I60-I66, G45) HF includes ICD-10 codes: I50, I11.0, I13.0, I13.2) Chronic Kidney Failure includes ICD-10 codes: N17-N19, I12.0-I12.9, I13.1, I13.2, N08.3, E11.2, E12.2, E13.2, E14.2, Z49, Z99.2
Intervention	SGLT-2 I or GLP-1 RA (Cohort 1 only) in addition to metformin as first line treatment	Evaluated as a drug family.
Comparator	Metformin first-line in combination with other glucose-lowering drugs	Best standard of care for diabetes treatment
Outcome	Primary outcomes were the incidence of overall mortality, CV-mortality, MI, stroke, HF and ESRD. Secondary outcomes were adverse events related to treatment (gastrointestinal events, hypoglycaemia, genital infections) and diabetes (ketoacidosis and amputations)	Measures of efficacy for both the intervention and comparator. These are the main endpoints able to reflect the therapeutical efficacy.

3.2 Exclusion criteria

The exclusion criteria in this analysis were studies of populations with no established disease (i.e., neither cardiovascular nor renal) and studies in a language other than English.

3.3 Literature search

The search was performed in the PUBMED database using the following search strategy of MeSH terms: "diabetes mellitus" AND "SGLT-2" AND "metformin" OR "GLP-1" AND "Metformin" AND "cardiovascular disease" AND "renal disease". Meta-analyses, cohort studies and clinical trials from 2016 to 2021 were selected. Studies published in the Nordic countries, especially Norway, were selected by performing a search in the PUBMED database (no MeSH terms were used for this search).

The definition of the endpoints for the analysis was done through a close collaboration with the Directorate of Health. The endpoints or outcomes were agreed based on the expected effect that SGLT-2 inhibitors and GLP-1 RAs would have in diabetic patients with established cardiovascular or chronic kidney disease already treated with metformin. These two drug classes have shown beneficial effects on overall mortality (SGLT-2 i), CV mortality (SGLT-2 i and GLP-1 RA) and the incidence of cardiovascular and renal events, independent of the serum glucose level in patients with T2DM.

3.4 Study selection

From the initial selection of 60 studies, 3 were taken as the main source of data inputs. Three network metanalyses — Li et al (2021), Palmer et al. (2021) and Tsapas et al. (2020) — and one multinational cohort study by Birkeland et al. (2020). Li et al. and Palmer et al. seem overlap as the numbers are derived from the "magic app." The lists of studies included in both network meta-analyses were reviewed to select the potential clinical trials that could be relevant for the analysis. Results included estimated absolute effects of treatment per 1000 patients treated for five years. In this analysis, the five-year estimates were converted into one-year rates and probabilities.

3.4.1 Cohort 1 – T2DM with established CVD

We decided to use the three most recent, Li et al. (2021), Palmer et al. (2020) and Tsapas et al. (2020). These two meta-analyses were more extensive than, for instance, Kristensen et al. (2020) and McGuire et al. (2020).

3.4.2 Cohort 2 – T2DM with establisehd CKD

The estimates for the efficacy of addition therapy with GLP-1 RA for diabetic patients with a history of renal disease and/or HF were taken from Li et al. (2021) and Palmer et al. (2020). These

meta-analyses were selected due to its subgroup analysis of T2DM patients with established renal disease, which allowed a refined estimation of the treatment effect.

3.4.3 Baseline probabilities

Information about baseline risks for Cohort 1 were collected from two clinical trials, EMPA-REG (Wiviott et al., 2019) and DECLARE–TIMI 58 (Zelniker et al., 2019). These two studies consisted of similar patient cohorts—T2DM with established CVD and T2DM with established CKD—and included cardiovascular and renal outcomes and mortality. Both studies included T2DM patients with established cardiovascular disease, where the mean ages were 63.9±6.8 (DECLARE–TIMI 58) and 63.1 ± 8.6 (EMPA- REG).

In addition, searches were performed for information about adverse events, such as genital infections, microvascular complications and gastrointestinal events (Baena Diez et al., 2016). The prevalence of amputations in Norwegian patients with diabetes was taken from Slåtsve et al. (2020), who described the total prevalence of diagnosed diabetes and the quality of care in Norway.

The multinational cohort study by Birkeland et al. (2020) provided baseline estimates for a Norwegian population of patients with type 2 diabetes treated with blood glucose lowering agents on the prevalence of cardiovascular and renal disease in diabetic patients. Information on the prevalence of diabetes patients with CVD or CKD was taken from the Norwegian ROSA 4 study (Rosa-4 study, 2019).

3.5 Assessment of Risk of Bias (RoB) in included studies

The evidence for Cohorts 1 and 2 was taken mainly from the network analysis by Li et al. (2021) and Palmer et al. (2020). This included clinical trials from different countries as well as multinational studies. It is important to take this into consideration given the differences in genetics, disease prevalence and incidence between these countries and Norway. The transferability of the study to the Norwegian setting might represent a source of bias.

3.6 Assessment of the certainty of the evidence

The assessment of the certainty of the evidence were based on the GRADE approach (Grading of Recommendations Assessment, Development and Evaluation), developed by the GRADE working group, to assess the quality of the evidence. Only main clinical outcomes were graded. GRADE evaluates the quality of the evidence separately for each outcome of interest, and is expressed either as high, moderate, low, or very low.

The certainty of the evidence is defined as:
High certainty ⨁⨁⨁⨁: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty ⨁⨁⨁◯: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty ⨁⨁◯◯: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty ⨁◯◯◯: We have very little confidence in the effect of the estimate: The true effect is likely to be substantially different from the estimate of effect.

Results from RCT's begin with a rating of high certainty evidence. This may be downgraded according to five criteria: 1) risk of bias as assessed by review authors. 2) degree of inconsistency (unexplained heterogeneity between studies), 3) indirectness (indirect comparisons; issues related to the generalizability of findings), 4) imprecision of estimates, and 5) presence of reporting bias. Observational studies begin with a rating of low certainty evidence. The level of certainty can also be upgraded when results show a large effect estimate, or a dose- response gradient, or if all possible confounders would likely only diminish the observed effect.

3.7 Results of the search

In the next section we will present the efficacy and adverse events for the two cohorts. For Cohort 1, we present both estimated efficacy from Palmer et al. (2021) and from Tsapas et al. (2020), while for Cohort 2, we have only applied data from Palmer et al. (2021). For adverse events, we have also collected information from other sources (also reported in the method section). The evaluations of the GRADE were based on that reported in Li et al. (2021) and Palmer et al. (2020).

3.7.1 Cohort 1 – efficacy

Table 2: Cohort 1 health outcomes for Metformin and SGLT2 i versus Metaformin with other glucose-lowering drugs. Results based on the meta-analysis by Li et al (2021) and Palmer et al (2020)

Outcome	Study results and outcomes	Absolute effect estimates (5 years) per 1000		Certainty of evidence (GRADE)
		Standard of care	SGLT2 i	
All-cause mortality	OR 0.77 (CI 0.71-0.83), n=282704, no studies 225	120	95 25 fewer (CI 32 to 18 fewer)	Moderate (due to serious imprecision)
Cardiovascular mortality	OR 0.84 (CI 0.76-0.93), n=222944, no studies 128	79	67 12 fewer (CI 18 to 6 fewer)	Moderate (due to serious imprecision)
Non-fatal myocardial infarction	OR 0.87 (CI 0.79-0.97), n=262168, no studies 199	108	95 13 fewer (CI 21 to 3 fewer)	Moderate (due to serious imprecision)
Non-fatal stroke	OR 1.01 (CI 0.89-1.14), n=257767, no studies 171	108	109 1 more (CI 11 fewer to 13 more)	High
End-stage kidney disease	OR 0.71 (CI 0.57-0.89), n=79876, no studies 31	20	14 6 fewer (CI 9 to 2 fewer)	High
Hospital admission for heart failure	OR 0.70 (CI 0.63-0.77), n=229615, no studies 141	80	57 23 fewer (CI 28 to 17 fewer)	High

Table 3: Cohort 1 health outcomes for metformin and SGLT2 i versus metformin with other glucose-lowering drugs Results based on the meta-analysis by Tsapas et al 2020

Outcome	Study results and outcomes	Certainty of evidence (GRADE)
All-cause mortality	OR 0.86 (CI 0.77-0.96). no. of studies 51	Moderate (due to serious imprecision)
Cardiovascular mortality	OR 0.85 (CI 0.74-0.97). no. of studies 51	Moderate (due to serious imprecision)
Non-fatal myocardial infarction	OR 0.92 (CI 0.83-1.01) no. of studies 51	Moderate (due to serious imprecision)
Non-fatal stroke	OR 1.01 (CI 0.89-1.14) no. of studies 51	Moderate (due to serious imprecision)
End-stage kidney disease	OR 0.63 (CI 0.50-0.79) no. of studies 51	High
Hospital admission for heart failure	OR 0.72 (CI 0.65-0.80) no. of studies 51	Moderate (due to serious imprecision)

Table 4: Cohort 1 health outcomes for metformin and GLP-1 RA versus metformin with other glucose-lowering drugs. Results based on the meta-analysis by Li et al (2021) Palmer et al (2020)

Outcome	Study results and outcomes	Absolute effect estimates (5 years) per 1000		Certainty of evidence (GRADE)
		Standard of care	SGLT2 i	
All-cause mortality	OR 0.88 (CI 0.83-0.94), n=69035, no studies 34	120	107 13 fewer (CI 18 to 6 fewer)	Moderate (due to serious imprecision)
Cardiovascular mortality	OR 0.88 (CI 0.80-0.96), n=63455, no studies 20	79	70 9 fewer (CI 15 to 3 fewer)	Moderate (due to serious imprecision)
Non-fatal myocardial infarction	OR 0.92 (CI 0.85-0.99), n=67956, no studies 32	108	100 8 fewer (CI 15 to 1 fewer)	Moderate (due to serious imprecision)
Non-fatal stroke	OR 0.84 (CI 0.76-0.93), n=66900, no studies 29	108	92 16 fewer (CI 24 to 7 fewer)	Moderate (due to serious imprecision)
End-stage kidney disease	OR 0.78 (CI 0.67-0.92), n=10762, no studies 4	20	16 4 fewer (CI 7 to 2 fewer)	High
Hospital admission for heart failure	OR 0.94 (CI 0.85-1.03), n=46696, no studies 13	80	76 4 fewer (CI 11 fewer to 2 more)	Moderate (due to serious imprecision)

Table 5: Cohort 1 health outcomes for metformin and GLP-1 RA versus metformin with other glucose-lowering drugs Cohort Results based on the meta-analysis by Tsapas et al 2020

Outcome	Study results and outcomes	Certainty of evidence (GRADE)
All-cause mortality	OR 0.87 (CI 0.79-0.96). no. of studies 58	Moderate (due to serious imprecision)
Cardiovascular mortality	OR 0.87 (CI 0.77-0.99). no. of studies 58	Moderate (due to serious imprecision)
Non-fatal myocardial infarction	OR 0.95 (CI 0.88-1.03) no. of studies 58	Moderate (due to serious imprecision)
Non-fatal stroke	OR 0.84 (CI 0.75-0.93) no. of studies 58	Moderate (due to serious imprecision)
End-stage kidney disease	OR 0.84 (CI 0.64-1.11 no. of studies 58	High
Hospital admission for heart failure	OR 0.93 (CI 0.85-1.03) no. of studies 58	Moderate (due to serious imprecision)

3.7.3 Cohort 2 – efficacy

Table 6: Cohort 2 health outcomes for metformin and SGLT-2 inhibitor versus metformin with other glucose-lowering drugs. Li et al (2021) Palmer et al (2020)

Outcome	Study results and outcomes	Absolute effect estimates (5 years) per 1000		Certainty of evidence (GRADE)
		Standard of care	**SGLT2 i**	
All-cause mortality	OR 0.77 (CI 0.71-0.83), n=282704, no studies 225	170	136 34 fewer (CI 43 to 25 fewer)	High
Cardiovascular mortality	OR 0.84 (CI 0.76-0.92), n=222944, no studies 128	112	96 16 fewer (CI 25 to 8 fewer)	High
Non-fatal myocardial infarction	OR 0.87 (CI 0.79-0.97), n=262168, no studies 199	120	106 14 fewer (CI 23 to 3 fewer)	High
Non-fatal stroke	OR 1.01 (CI 0.89-1.14), n=257767, no studies 171	120	121 1 more (CI 12 fewer to 15 more)	High
End-stage kidney disease	OR 0.71 (CI 0.57-0.89), n=79876, no studies 31	92	67 25 fewer (CI 37 to 9 fewer)	Moderate (due to serious imprecision)
Hospital admission for heart failure	OR 0.70 (CI 0.63-0.77), n=229615, no studies 141	105	76 29 fewer (CI 36 to 22 fewer)	High

3.7.4 Adverse events

Table 7: Cohort 1 health outcomes for metformin and SGLT-2 inhibitor versus metformin with other glucose-lowering drugs, including GRADE and source for evidence

Outcome	**Study results and outcomes**	**Absolute effect estimates (5 years) per 1000**		**Certainty of evidence (GRADE)**	**Source**
		Standard of care	**SGLT2 i**		
Diabetic Ketoacidosis	OR 1.04 (0.61-1.78), n=98634, no studies 26	2	2 0 more per 1000 (from 1 fewer to 2 more)	Moderate due to serious imprecision	Palmer et al, 2021
Genital Infection	OR 3.5 (3.01-4.07), n=80771, no studies 78	73	216 143 more (CI 119 more- 170 more)	High	Palmer et al, 2021
Gastrointestinal Events	OR 0.92 (0.85-0.99), n=67956, no studies 32	No important difference		N/A	Li et al., 2021
Amputation	OR 1.1(0.95-1.77)	45	50 6 more per 1000 (from 2 fewer to 16 more)	Moderate due to serious imprecision	Palmer et al, 2021
Microvascular	OR 0.91 (0.88-0.94)	*		N/A	Tsapas et al, 2020
Hypoglycemia	OR 0.90 (0.70-1.16)	25	23 2 fewer per 1000 (from 8 fewer to 4 more)	High	Palmer et al, 2021

*Note. * = not available*

Table 8: Cohort 1 health outcomes for metformin and GLP-1 RA versus metformin with other glucose-lowering drugs. , including GRADE and source for evidence

Outcome	Study results and outcomes	Absolute effect estimates (5 years) per 1000		Certainty of evidence (GRADE)	Source
		Standard of care	GLP-1 RA		
Diabetic Ketoacidosis	OR 0.50 (0.45- 0.55)	2	1 1 fewer per 1000	High	Palmer et al, 2021
Genital Infection	OR 0.71(0.34- 1.44)	73	52 21 fewer per 1000 (from 47 fewer to 29 more)	Moderate due to serious imprecision	Palmer et al, 2021
Gastrointestinal Events	OR 2.46 (1.22-4.97), n=24638, no studies 7	44	102 58 more (CI: 9 more- 142 more)	Low due to inconsistency and serious imprecision	Li et al., 2021
Amputation	OR 0.33 (0.01-8.18)	45	15 30 fewer per 1000 (from 45 fewer to 324 more)	Low due to very serious imprecision	Palmer et al, 2021
Microvascular	OR 1.18 (1.15- 1.22)	*		N/A	Tsapas et al, 2020
Hypoglycemia	OR 0.9 (0.79-1.08)	25	24 2 fewer per 1000 (from 5 fewer to 7 more)	Moderate due to serious imprecision	Palmer et al, 2021

*Note. * = not available*

Table 9: Cohort 2 health outcomes for metformin and SGLT2 inhibitor versus metformin with other glucose-lowering drugs. , including GRADE and source for evidence

Outcome	Study results and outcomes	Absolute effect estimates (5 years) per 1000		Certainty of evidence (GRADE)	Source
		Standard of care	SGLT2 i		
Diabetic Ketoacidosis	OR 1.04 (0.61-1.78)	2	2 0 more per 1000 (from 1 fewer to 2 more)	Moderate due to serious imprecision	Palmer et al, 2021
Genital Infection	OR 3.50 (3.01-4.07)	73	216 143 more (from 119 more to 170 more)	High	Palmer et al, 2021
Gastrointestinal Events	N/A	No important difference		N/A	Li et al., 2021
Amputation	OR 1.1 (0.96-1.35)	55	61 8 more per 1000 (from 2 fewer to 19 more	Moderate due to serious imprecision	Palmer et al, 2021
Microvascular	OR 0.91 (0.88-0.94)	*		N/A	Tsapas et al, 2020
Hypoglycemia	OR 0.90 (0.70-1.16)	25	23 2 fewer per 1000 (from 8 fewer to 4 more)	High	Palmer et al, 2021

*Note. * = not available*

4. Methods

4.1 Population

The study includes two patient populations. All patients are at least 60 years old with T2DM. In addition, the population was further divided in two groups according to the established disease:

1) Cardiovascular (CV), where CV disease included 1) myocardial infarction, 2) stroke (hemorrhagic or ischemic) and 3) heart failure (HF) (from CV etiology) – ICD-10 codes (Cohort 1)
2) Chronic kidney disease (CKD) and/or HF (from renal etiology) – ICD-10 codes (Cohort 2)

4.2 Intervention

We evaluated two treatment options, sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists added to metformin as first-line treatment of patients with T2DM.

Cohort 1, the T2DM with established CV, were eligible for both SGLT-2 i and GLP-1 RA, while Cohort 2 were only eligible for SGLT- 2 inhibitors.

4.3 Comparator

The standard of care for patients with T2DM, which consisted of metformin as the first line of treatment. In patients where metformin might be contraindicated or in those who did not reach the HbA1c target (≤ 8%), second-line treatment was offered. This consisted of any of the following: 1) sulfonylurea, 2) DPP-4 inhibitors, 3) SGLT-2 inhibitors, 4) GLP-1 RA, 5) thiazolidinediones or 6) insulin.

4.4 Outcomes

Quality-adjusted life years (QALYs) and life years (LYs) were the primary health outcome measures. The number of events and adverse events related to treatment were also quantified to assess the treatment effect of both the intervention and comparator. Events were defined as any of the following: 1) myocardial infarction (MI), 2) stroke (ischemic or hemorrhagic), 3) any decrease from baseline eGFR, 4) any diabetes-related complication, 5) hospitalization for heart failure (HHF), 6) all-cause mortality and 7) CV mortality. Adverse events included were gastrointestinal events, hypoglycemia, genital infection, microvascular, ketoacidosis and amputation.

The main outcome of the analysis is the cost-effectiveness (see Section 2.2 for details) of SGLT-2 i and GLP-1 RA compared to metformin only as first-line treatment. The results will be presented

by the ICER (see Section 2.2) and CEACs. Finally, the budget consequences are presented in a budget impact analysis.

4.5 Model

To evaluate the cost-effectiveness, we developed different models for the two cohorts. For Cohort 1 (CV disease) a combination of a decision tree and a Markov model (Figures 2 and 3) was applied to model the treatment pathway from first-line treatment. Both models were combined to account for the consequences of short-term events and additional long-term consequences of additional CV events (MI, stroke, and HF), chronic kidney disease, ESRD, CV mortality and all-cause mortality (without CV mortality).

The model for the treatment pathway for Cohort 2 (renal and/or HF) consisted of a Markov model, which accounted for acute and chronic kidney disease, ESRD, ESRD and HF, in addition to CV events, all-cause mortality (without CV mortality) and CV mortality.

The models include long-term consequences of 30 years with yearly cycles.

4.5.1 Model Cohort 1 – T2DM and CVD

Two models were developed to capture the complex pathway of patients in Cohort 1, presented in Figures 2 and 3. Figure 2 is an integrated part of Figure 3, where Figure 2 illustrates the one-year events for patients with T2DM with established CVD (the circle T2DM + CVD occurs in both figures) that have not experienced any additional events. The decision tree in Figure 2 includes one year CV and renal events for individuals that have not yet experienced any additional CV or renal events, while Figure 3 represents the long-term consequences after experiencing additional events (defined by Figure 2). Ovals represent health states, rectangles represent events, while arrows represent movements.

All patients in Cohort 1 start in the health stage (defined by the circle in Figures 2 and 3) *T2DM + CVD*. This health state includes only individuals who have not yet experienced any additional events (MI, stroke, HF or chronic kidney disease). During one cycle (one year), an individual can die from all causes (except CVD), experience an event (MI, stroke, HF or chronic kidney disease) and die from CV. In addition, all individuals except those dying from all causes (without CV mortality), could experience an adverse event (ketoacidosis, genital infection, hypoglycemia, microvascular or amputation). Individuals with *no event* during one cycle will return to the health state *T2DM + CVD* and in the next cycle (year) will have the risk of an CV or CKD event. An

individual with an *MI* event in the decision tree who does not die within the first year will enter the health state *post MI* in Figure 3. Similarly, an individual who experiences a *Stroke* and does not die within the first year will either be allocated to *Stroke without sequel*, *Moderate Stroke* or *Severe Stroke* in Figure 3. Similar movements were observed for *HF* and *Chronic Kidney disease*. All patients can experience T2DM adverse events, independent of events (no event, MI, Stroke, HF or Chronic Kidney disease).

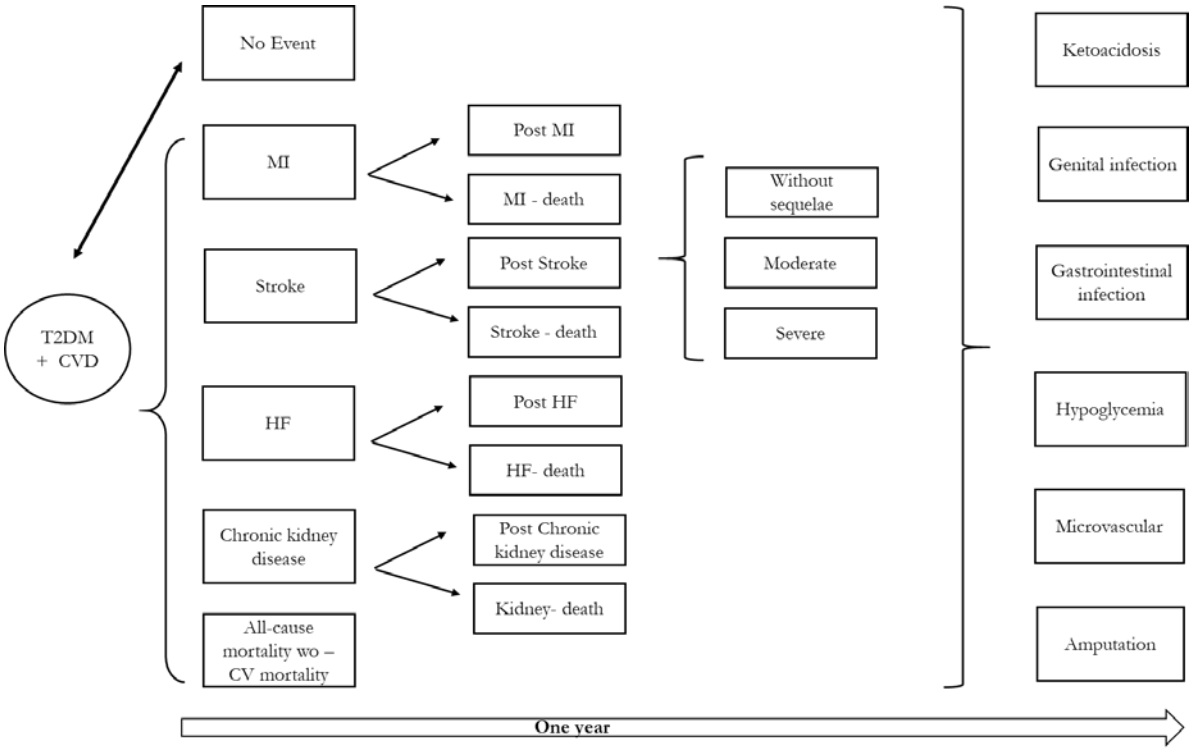

Figure 2: Decision tree for Cohort 1 (established CV disease), where the rectangles are events, ovals are Markov health states and arrows indicate movements between events.

Patients surviving a particular event would then progress to one of the Markov model health states (see Figure 3) in the subsequent cycle: (i) *Post MI*, (ii) *Stroke without sequel*, (iii) *Moderate stroke*, (iv) *Severe Stroke*, (v) *Post HF*, (vi) *Post Chronic Kidney disease* (vii) *All cause death excluding CV causes* and (viii) *CV mortality*. The Markov model captures the long-term consequences of treatment for health outcomes, adverse events and mortality. Oval circles represent health states, rectangles represent events, arrows represent movements and clams are used to illustrate movements from or to multiple events or health states.

From all health states, patients can experience additional events, such as death (CV, kidney or all causes) or staying in the same health state. An individual experiencing a new event and not dying

from it would move to the new health state in the following cycle. For example, an individual in *Post MI*, who experienced a stroke without sequel and survived, would move to the health state *Stroke without sequel* in the following cycle. Of note, individuals in the *Post HF* who experience an acute kidney injury (AKI), would move to *Post chronic kidney disease*. Only patients in *Post chronic kidney disease* can move to *Post ESRD* (i.e., renal disease that needs dialysis or kidney transplant). By including several health states, disease history was partly accounted for, such as the probability of an MI for individuals with a moderate stroke.

Individuals can experience any T2DM-related adverse event (to the right in the figure) in all health states. Those surviving the adverse event, move back to the health state in which they had experienced the adverse event. For instance, an individual in *Post MI* who experienced hypoglycemia and survived moves back to *Post MI* in the following cycle. Patients who did not survive the adverse event moved to death (classified as death from all-causes).

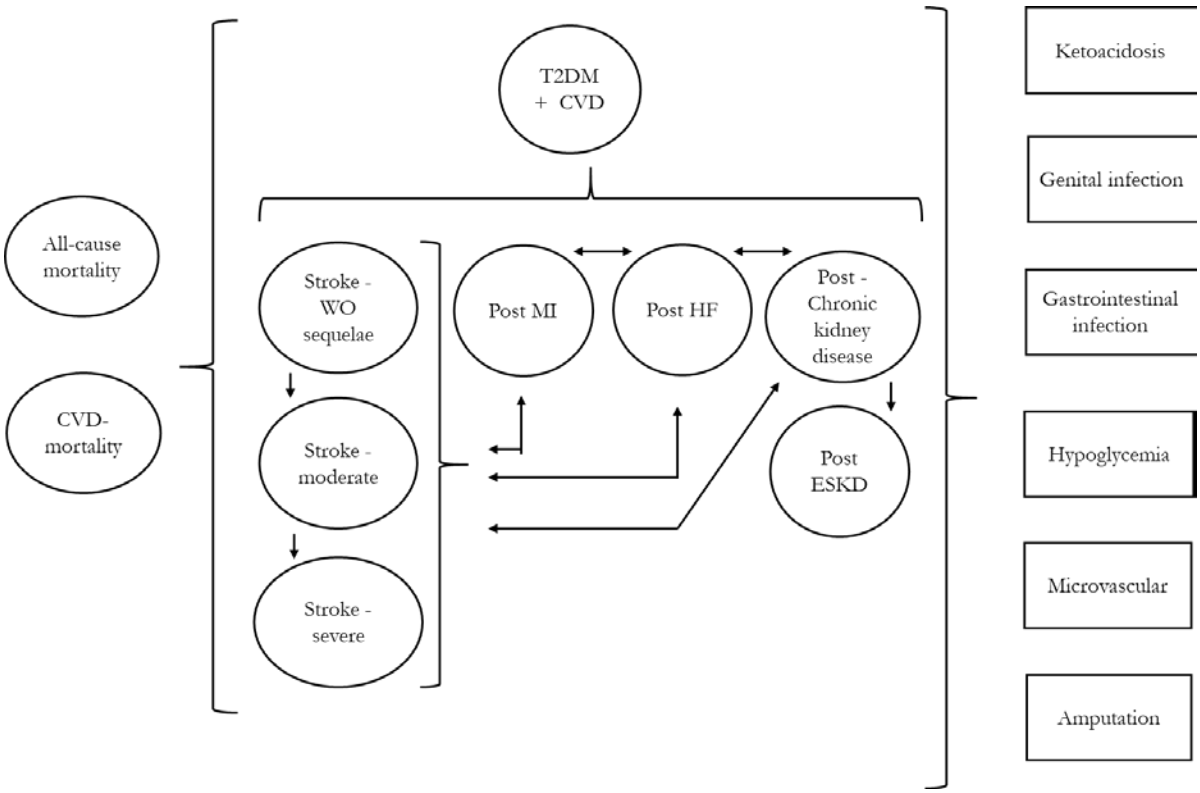

Figure 3. Markov Model for Cohort 1 illustrating the different health states (ovals) and adverse events (squares). Patients in any health state could experience any of the adverse events. Include the survivors to show link to decision tree

4.5.2 Model Cohort 2 – T2DM and CKD

A Markov model was developed to account for baseline risks and probabilities of events for individuals with T2DM and CKD. For this cohort of patients, we let the kidney disease dominate the health states and included the CVD as events within a health state.

The model consisted of four health states, 1) *T2DM + CKD w/ or w/o HF*, 2) *Post ESKD*, 3) *Post HF after ESKD* and 4) *Death* (further divided into all causes, without CV, CV death and death from cancer) (Figure 4). Cohort 2 started in the health state *T2DM + CKD w/ or w/o HF*. From that health state, the individual could either stay, move to *Post ESKD* or die. Someone in *Post ESKD* could either stay, move to *Post ESKD + HF* after experiencing a HF or die. In *Post ESKD + HF,* a patient could either stay there or die. From all health states, the individuals could experience the CV events of MI, Stroke and HF. Except for HF in *Post ESKD*, these events are included in the model with additional costs related to the event.

As for Cohort 1, adverse events related to T2DM (right side of the model) could occur in any health state. Patients who experienced an adverse event and survived moved in the next cycle back to the health state in which they had experienced the adverse event (such as *Post ESKD).*

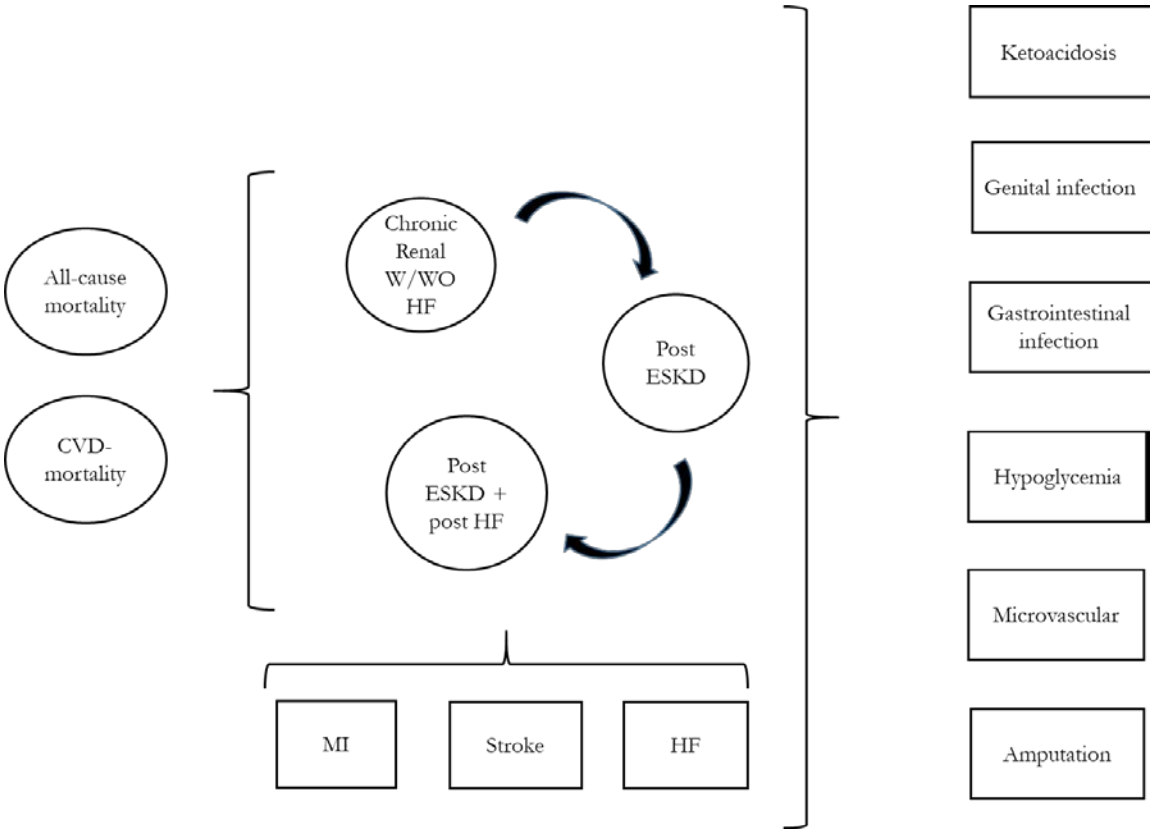

Figure 4. Markov Model for the Cohort 2 (Renal and/or HF) illustrating the different health states (ovals) and adverse events (squares). Patients in any health state could experience any of the adverse events

4.6 Time Horizon

The model was developed within a time horizon of 30 years, with a maximal age limit of 90 years old.

4.7 Perspective

A healthcare perspective was chosen, as recommended in Norwegian guidelines (NOMA, 2020). This included all costs related to medical treatment, follow-up consultations at the outpatient clinic, and treatment costs according to the event.

4.8 Data input

Based on the literature search, we used several sources for baseline probabilities. However, three main network meta-analyses were used to elicit the baseline probabilities and odds ratios for treatment effect in both cohorts: Tsapas et al. (2020), Li et al. (2021) and Palmer et al. (2020). The choice of source was made upon whether the value was available or significant enough to be used. In cases where values were neither significant nor available in these three meta-analyses, other sources were used (see Appendix A1).

4.8.1 Transition probabilities

Baseline probabilities and risks for both cohorts were applied. For the CV cohort, the baseline probabilities used in the decision tree are shown in Table 3. The transition probabilities for the CKD (Cohort 2) are presented in Appendix A1. These were directly extracted from Palmer et al. (2020).

The main assumption for both the CV and CKD cohorts was that patients with an established disease have already experienced an event when entered to the decision tree and Markov model, respectively. Age-adjusted baseline probabilities of events were used only for MI, HF and stroke in each cohort, whereas probabilities of adverse events and CKD were not age-adjusted and assumed to be constant over time for both cohorts.

Additionally, the baseline age-adjusted probabilities were further adjusted with the relative risks (RR) based on their specific assumption of previous history of an event, as these were not identified in the literature (see Table 4) (i.e., an RR of a patient with a history of HF experiencing MI or a patient with MI history experiencing a HF based on their established disease group). These relevant relative risks (RR) were applied to account for high CV risk for a range of possible preceding events (MI, HF, Stroke or Stroke after a Stroke). Due to variations in patient history based on the established disease, each cohort had a different RR adjustment to their baseline probabilities for an additional CV or renal event.

Table 10: Baseline probabilities of events for Cohort 1(T2DM with established CV)

Baseline Probability	Cohort 1: CVD	Source
Myocardial Infarction	0.019	Zelniker et al, 2019
Stroke	0.009	Zelniker et al, 2019
Stroke without sequel	0.005	*
Stroke w/moderate sequel	0.003	*
Stroke w/severe sequel	0.001	*
Heart Failure	0.014	Zelniker et al, 2019
Hypoglycemia	0.100	Zelniker et al, 2019
Ketoacidosis	0.0003	Zelniker et al, 2019
Amputation	0.010	Slåtsve et al.,2020
Chronic Kidney Disease	0.005	Zelniker et al, 2019
End Stage Renal Disease	0.004	Wiviott et al.,2019
Genital Infection	0.006	Zelniker et al, 2019
Cancer	0.014	Wiviott et al.,2019
CV Death	0.007	Zelniker et al, 2019
All- Cause Death	0.020	Zelniker et al, 2019

Note. * Calculated with additional probabilities of events, see Appendix A1

Table 11: Baseline relative risks for events according to cohort

Relative Risk	Cohort 1 - CVD Group	Source	Cohort 2: CKD group	Source
Heart Failure	2.09	Swedeheart Study	2.09	Birkeland et al.,2020
MI	1.45	Birkeland et al.,2020	1.6	Birkeland et al.,2020
Stroke	1.74	Birkeland et al.,2020	1.23	Birkeland et al.,2020
Death from Genital Infections	1.72	Baena Díez et al., 2016	1.72	Baena Díez et al., 2016
Death from Gastrointestinal Events	4.33	Baena Díez et al., 2016	4.33	Baena Díez et al., 2016
Death from Microvascular Complications	4.2	Baena Díez et al., 2016	4.2	Baena Díez et al., 2016
CV death	*		1.87	Birkeland et al.,2020
All- cause death	*		2.06	Birkeland et al.,2020

*Note. * = Mortality estimates were retrieved from Norwegian mortality tables.*

4.8.1.1Cohort 1 – (T2DM and CVD)

Baseline probabilities of events for diabetic patients with CV disease history were taken from different clinical trials (Table 10). The transition probability for allocating patients into (i) stroke

without sequel, (ii) moderate stroke and (iii) severe stroke was derived from the literature, conditional on all stroke events in the baseline probabilities for the decision tree (Appendix A1*). These probabilities were then combined with the relevant RR to elicit the transition probability from one health state to another (Appendix A1). RRs were applied to account for the high CV risk of the patient population for a range of possible events, as presented in Table 4. For example, the probability of HF in a diabetic patient with CV risk was calculated by multiplying the baseline probability of HF in the general diabetic population by the RR of HF in patients with both diabetes and CV disease history (i.e., 0.01*2.09= 0.03). If after the event the patient survived, the probability of going back to a *Post HF* health state the next cycle was calculated as *1- Probability of death from CV causes for a patient of the same age.*

4.8.1.2 Cohort 2 (T2DM – CKD)

Baseline probabilities of events for diabetic patients with established CKD were taken from Li et al. (2021) and Palmer et al. (2020). These authors provided the adjusted probability of event (MI, HF, stroke, ESKD and adverse events) for a diabetic patient with CKD. This contributed to the accuracy of the model for reflecting the cumulative probability of events in patients with multiple comorbidities. The probability of surviving and then returning to the initial health state was calculated with the same method as for the CV group.

4.8.2 Adverse events

All patients can experience any of the following diabetes-related complications: microvascular complications (diabetic mono/polyneuropathy, diabetic eye complications, diabetic foot/peripheral angiopathy, diabetic kidney disease, diabetes with several/unspecified complications), peripheral artery disease, ketoacidosis and lower limb amputations. Patients can also be treated for concomitant underlying conditions. Furthermore, the probabilities of adverse events were assumed to be constant over time and no cumulative risk was applied. Thus, the probability of having an adverse event in each cycle was not influenced by the occurrence of adverse events during past cycles.

4.8.3 Efficacy

The odds ratios (ORs) for the treatment effects of the intervention (combination therapy with GLP-1 RA or SGLT-2 i) were applied to both cohorts in all cycles, based on the established risk in both the decision tree and Markov model (see Table 12). The OR effect of GLP-1 RA was applied to those with established CV disease, whereas the OR for SGLT-2 I was applied to those

with established CKD. Likewise, the RR effect of GLP-1 RA and SGLT-2 i on survival mortality was also applied based on the relevant patient's survival from a specific CV, renal and other adverse events for five years consecutively in each of the high-risk groups.

Table 12. Odds Ratios for the Efficacy of GLP-1 RA and SGLT-2 i

Cohort	**Cardiovascular**				**Renal**
Comparison	GLP-1 RA vs. Standard of care		SGLT-2 i vs Standard of care		SGLT-2 i vs standard of care
Source	Tsapas	Palmer	Tsapas	Palmer	Palmer
All-cause mortality	**0.87**	0.88	**0.86**	**0.77**	**0.82**
Cardiovascular mortality	**0.87**	0.88	**0.85**	0.84	**0.86**
Myocardial Infarction	0.95	0.92	0.92	0.87	0.89
Stroke	**0.84**	0.84	1.01	1.00	1.01
Hospitalization for Heart Failure	0.93	0.94	**0.72**	**0.70**	**0.74**
Adverse events					
Microvascular	-	1.18	-	0.90	0.90
Amputation	0.86	0.33	1.30	1.1	1.1
End Stage Renal Disease	0.84	**0.78**	**0.63**	**0.71**	**0.73**
Diabetic Ketoacidosis	-	**0.50**	-	**1.04**	**2.00**
Genital Infections	-	0.71	-	**3.50**	**2.90**
Hypoglycemia	0.86	0.90	1.30	0.90	**0.90**
Acute Kidney Injury	-	**0.86**		0.78	**0.75**
Gastrointestinal events	-	2.46	-	*	*

*Note. Odds ratios were taken from Tsapas et al. (2020) and Palmer et al. (2021) where GLP-1 and SGLT-2 are compared with placebo (metformin). Values in bold are considered as significant or as high certainty evidence. * = no important difference was found in these comparisons.*

To apply the treatment effect of GLP-1 RA and SGLT-2 I to the respective cohorts, the ORs were multiplied by the baseline probability of the event (adjusted for age and previous risks) in each cohort. In the main analysis, we assumed that the effect lasted over the life course.

4.8.4 Mortality

Mortality was taken from Norwegian life tables corresponding to the year 2021 (Statistics Norway, 2021). It was divided into 'All-cause mortality excluding CV causes' and 'CV mortality,' the former was applied to patients with adverse and chronic kidney events and the latter to patients with CV events. The mortality during the first year after an MI, HF or stroke event was assumed to be higher than the following years every time a patient entered a given health state.

4.8.5 Utility weights

To estimate QALYs for each alternative treatment, we assigned a utility weight to all health states and included disutility for the adverse events. The numbers applied are based on EQ-5D values,

which is in line with the Norwegian guidelines. To estimate the utility weight for having T2DM and CVD, we used the utility weight reported for T2DM patients (0.785 reported in Clarke et al 2002) and declines with the disutility of CVD (-0.108 from Nguyen et al 2018).

Table 13: Utility weights and disutility according to health state and event

Health state/event	Value/disutility	Source
Health states		
T2DM + CVD	0.677	Clarke et al 2002 and Nguyen et al 2018
T2DM + CKD	0.630	Clarke et al 2002 and
Post MI	0.622	Clarke et al 2002
Stroke without sequele	0.64 (0.48 – 0.80)	Nguyen et al 2018
Stroke moderate	0.50 (0.40 – 0.60)	Assumption
Stroke severe	0.36 (0.28 – 0.44)	Nguyen et al 2018
End stage kidney	0.505 (0.385 -0.625)	Clarke et al 2002 and Nguyen et al 2018
Heart failure (severe with kidney disease)	0.397 (0.44 -	
Events:		
Amputation (disutility)	-0.280 (-0.389 – -0.170)	Clarke et al 2002
Hypoglycemia (disutility)	-0.014	
Ketoacidosis (disutility)	-0.009	
Genital infections (disutility)	-0.003	
Gastrointestinal events (disutility)	-0.051	
Microvascular complications (disutility)	-0.091	Beaudet et al (2014)

4.8.6 Costs

Costs related to health states, events and medicines were calculated and inflated to the year 2021 when necessary, using the Inflation Calculator by SSB (2021). Costs were applied for all cycles in the model. Health states' costs were defined by the corresponding diagnosis-related group (DRG) when available or retrieved from the literature. These are yearly follow-up costs applied to each cycle. Events were classified as adverse events related to medical treatment (adverse events due to metformin, SGLT-2 i or GLP-1 RA), CV or renal events and diabetes-related events. Events' costs are calculated as the cost for the acute treatment of a given event.

Costs for all events were calculated with the corresponding DRG, except for MI and stroke costs, which were available in the literature and taken from Iversen et al. (2015) and the Norwegian Institute of Public Health, respectively. Drug costs were taken from the Norwegian Medicines Agency database (2021) and calculated as a one-year duration treatment (see Table 14).

To estimate the cost of treatment, we use the two most frequently used drugs in each group reported by the Norwegian Prescription Database (NorPD). Daily doses of empagliflozin (10 mg) and liraglutide (1.8 mg) were selected as SGLT-2 i and GLP-1 RA, respectively. The estimation of treatment costs for the comparator included the weighted cost of several glucose-lowering drugs based on the proportion of users reported in Birkeland et al. (2020). The cost of each drug was multiplied by the proportion of users of that same drug in the Norwegian population. Thus, this cost included a combination of empagliflozin (10 mg), liraglutide (1.8 mg), metformin (1 g), glibenclamid (3.5 mg), linagliptin (5 mg), insulin (10 IE), and pioglitazone (15 mg). The treatment cost was applied for all cycles in the main analysis.

Table 14. Costs for health states, events and drugs. Costs for events are provided per event and then early follow-up costs.

Costs	Value	Description	Source
PostMI first year	kr 19,179	Costs for the first year of treatment after MI. Cost includes initial in- hospital treatment and specialist follow- up.	Iversen et al 2015
PostMI after first year	kr 3,846	Follow- up cost one year after MI. Includes GP consultations and medical treatment.	NorCad
PostStroke WO sequel	kr 34,245	Treatment and follow- up cost for a stroke wo sequel	Korman, 2016
PostStroke w/mod. sequel	kr 77,102	Treatment, follow- up and rehabilitation cost for a stroke w/moderate sequel	Korman, 2016
PostStroke w/severe sequel	kr 1,103,427	Treatment, follow- up and rehabilitation cost for a stroke w/severe sequel	Korman, 2016
PostHF	kr 1,775	Follow-up at outpatient clinic after heart failure	DRG 905D
PostCKD	kr 1,635	Follow- up at outpatient clinic consultation	DRG 911A
PostESKD	kr 13,734	Dialysis treatment cost per week X 3	DRG 317
Events			
MI	kr 7,979	In- hospital treatment cost	Iversen et al, 2015
Stroke	kr 93,736	In- hospital treatment cost	NIPH
HF	kr 66,434	In- hospital treatment cost	DRG 127
Hypoglycemia	kr 48,027	Treatment cost for diabetes with complications	DRG 294C
Genital Infection	kr 1,870	Treatment cost for urinary infections with complications	DRG 911O
Gastrointestinal event	kr 1,775	Treatment cost for gastrointestinal disease	DRG 906O
Microvascular complications	kr 54,242	Treatment cost for neurovascular and microvascular disease	DRG 18 and 130
Ketoacidosis	kr 48,027	Treatment cost for diabetes with complications	DRG 294C
Amputation	kr 254,992	Cost for surgical procedure	DRG 113
AKI	kr 69,378	Treatment cost for acute renal failure	DRG 316
Drugs			
Metformin + follow op	kr 3,324	Joint cost for different glucose- lowering drugs*	NoMA, 2021
SGLT2 i	kr 6,990	Empafligflozin + Metformin cost for 360 days of 10 mg and 1000 mg respectively.	NoMA, 2021
GLP-1 RA	kr 36,022	Exenatide cost for 360 days of 10 mg + Metformin cost for 360 days of 10 mg and 1000 mg respectively.	NoMA, 2021

Note.= Includes the 1- year weighted cost of different glucose- lowering drugs based on the proportion of its users reported in Birkeland et al.(2020). This cost includes empagliflozin (10 mg), liraglutide (1.8 mg), metformin (1 g), glibenclamid (3.5 mg), linagliptin (5 mg), insulin (10 IE), and pioglitazone (15 mg).*

4.9 Scenario and sensitivity analysis

The main sensitivity analysis for the model output is the probabilistic sensitivity analyses where we assign a distribution to all parameters, either based on observed standard deviation from the literature or assuming a standard deviation about 15-20% of the observed mean value.

To explore the magnitude of some of the assumption applied in the model, we have included several additional one-way sensitivity analyses. We have estimated the impact of the following parameters on the ICER:

- Cost of SGLT-2 i and GLP-1 RA
- RR of CV mortality
- RR of all-cause mortality
- No discounting of health outcomes

4.10 Budget impact analysis

The budget impact analysis is conducted according to Norwegian guidelines (NOMA, 2021). In the budget impact analysis we need to specify the number of patients that will use the drugs and competing drugs for the next five years, if the drugs are being reimbursed. Number of patients that will be using the drugs for the next five years if the drugs are not reimbursed should also be presented.

In 2020 about 220 000 individuals were living with diagnosed T2DM, which is expected to be higher if those not diagnosed had been included (https://www.fhi.no/nettpub/hin/ikke-smittsomme/diabetes/).

For the purpose of the budget impact analysis, we use the number of those diagnosed. It is expected that this number will increase (net of incidence and mortality), hence we apply a 3% increase. For the prevalence of the combined populations for Cohort 1 and Cohort 2 we have used data from the Rosa 4 study, reporting a prevalence of T2DM + CVD Rosa 4 study 24.6% of T2DM patients and 16.3 % in T2DM + CKD Rosa 4 study (Rosa 4 study – yearly report, 2019). It is assumed that there is an overlap of 11% between the two Cohorts, resulting in 29.9% patients in either Cohort 1 or 2 (24.6%+16.3%-11%=29.9%).

For current number of users of SGLT-2 i, GLP-1 RA, SU and DPP-4 i we apply information from the Norwegian Prescription Register (Appendix). There the number of current users of

SGLT-2 i, GLP-1 RA, DPP-4 *i* and SU were in 2020, 37 639, 31 582, 28 246 and 21 066 users, respectively. How many of these that belong to either Cohort 1 or 2 is not published, hence we will apply both an assumption of 30% and 50% current users in Cohort 1 and 2.

We also estimate the consequences of reimburse SGLT-2 i and/or GLP-1 RA on other health care costs. These costs includes the cost of treatment of cardiovascular and renal events and adverse events.

5. Results

5.1 Cost-effectiveness analysis

Based on the model estimates the costs, health outcomes and incremental values are presented in Table 15 and 16. For Cohort 1,

Table 15: Discounted Costs, LY and ICER for Cohort 1 (T2DM with established CV disease). Numbers in NOK

Intervention	Costs	Incr. Costs	Life Years	QALY	Incr. LY	Incr. QALY	ICER-LY(next lowest cost)	ICER-QALYs	ICER LY (metaf.)	ICER - QALYs (metaf.)
Metformin	291,356		11,15	7.02						
SGLT-2	338,588	47,232	11,94	7.54	0,79	0.53	59,811	89,517	59,811	89,517
GLP-1	608,268	269,680	11,56	7.32	-0,38	-0.23	(domin.)	(domin.)	768,499*	1,058,591

*The ICER is given by (608,268-291,356)/(11,56-11,15)

From Table 15 the cost-effectiveness results for Cohort 1 is presented. The costs is higher for SGLT-2 i and GLP-1 RA than metformin (NOK 338,588 for SGLT2 i, NOK 608,268 for GLP-1 RA and NOK 291,356 for metformin). Discounted life-years were higher for SGLT-2 i (11.94 LY) and GLP-1 RA (11.56 LY) than metformin (11.15 LY), and the trend was similar for QALYs, SGLT-2 i (7.54 QALYs) and GLP-1 RA (7.32 QALYs) than metformin (7.02 QALYs). When comparing all three treatment groups, SGLT-2 i is the preferred alternative (ICER NOK 59,811 per LY gained and NOK 89,517 per QALY gained), and is dominating GLP-1 RA as SGLT-2 I resulted in higher health outcomes than GLP-1 RA. When compared to metformin, GLP-1 RA has an ICER of NOK 768,499 per LY gained and NOK 1,058,591 per QALY gained.

Table 16: Discounted Costs, LY and ICER for Cohort 2 (T2DM with renal and/or HF). Numbers in NOK

Intervention	Costs	Incr. Costs	Life Years	QALY	Incr. LY	Incr. QALYs	ICER-LY	ICER-QALYs
Metformin	258,527		10.16	6.05				
SGLT-2	282,746	24,219	10.29	6.19	0.13	0.14	168,872	193,656

From Table 16 the cost-effectiveness results for Cohort 2 is presented. The costs are higher for SGLT-2 i than metformin (NOK 282,746 SGLT2 i and NOK 258,527 for metformin). Discounted life-years were higher for SGLT-2 i (10.29 LY) than for metformin (10.16 LY), and the trend was similar for QALYs, SGLT-2 i (6.19 QALYs) and metformin (6.05 QALYs). When comparing all three treatment groups, comparing SGLT-2 i to metformin results in an ICER of NOK 168,872 per LY gained and NOK 193,656 per QALY gained.
The recommendation depends on the threshold value for the two cohorts T2DM with either CVD or CKD.

From the Norwegian guidelines, the number of expected good years for an individual 60 years old is 19.8 years. Based on the estimation for metformin in the two models, we estimated the number of QALYs to 10.1 for Cohort 1 and 8.8 for Cohort 2, which provided a loss of 9.7 QALYs and 11.0 QALYs for Cohort 1 and 2, respectively. This indicate that they belong to group 3 (8 to 11.9), which in 2015 had a threshold of NOK475,000.

5.2 Sensitivity Analysis

Deterministic

We have evaluated how sensitive the ICER is to changes in the price of SGLT-2 i and GLP-1 RAs (Cohort 1, only). The price of SGLT-2 i varied from NOK 2000 to 9000 per year, while the price for GLP-1 RA was varied from NOK 20000 to 52500 per year.

For Cohort 1, we see that varying the price from NOK 2,000 to 9,000 per year, implied that the ICER was negative (cost-saving) for the lowest price and increased to around NOK 90,000 per QALY gained for the highest price. For GLP-1 RA, the ICER was around NOK 440,000 per QALY gained for the lowest price and increased to about NOK 1.7 million per QALY gained.

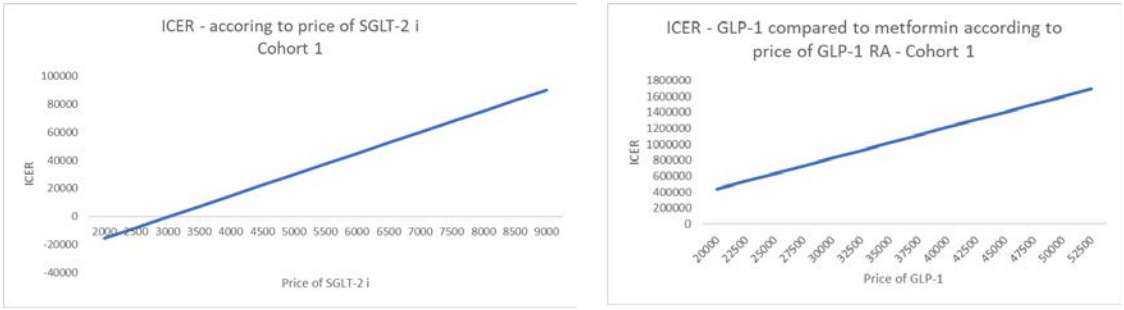

Figure 5: The effect of the price on SGLT-2 and GLP-1 on the ICER, when comparing with Metformin for Cohort 1.

For Cohort 2, varying the price on SGLT-2 i, resulted in ICER values from NOK-200,000 per QALY gained (cost-saving) for the lowest price to about NOK 360,000 per QALY gained for the highest price.

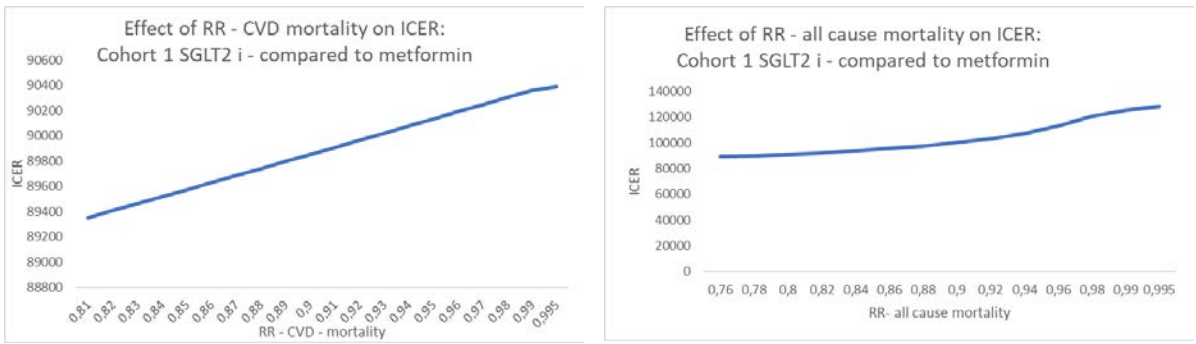

Figure 6: The effect of the RR risk of CVD mortality and all cause mortality of SGLT-2 i on the ICER, when SGLT2 i is compared with Metformin for Cohort 1.

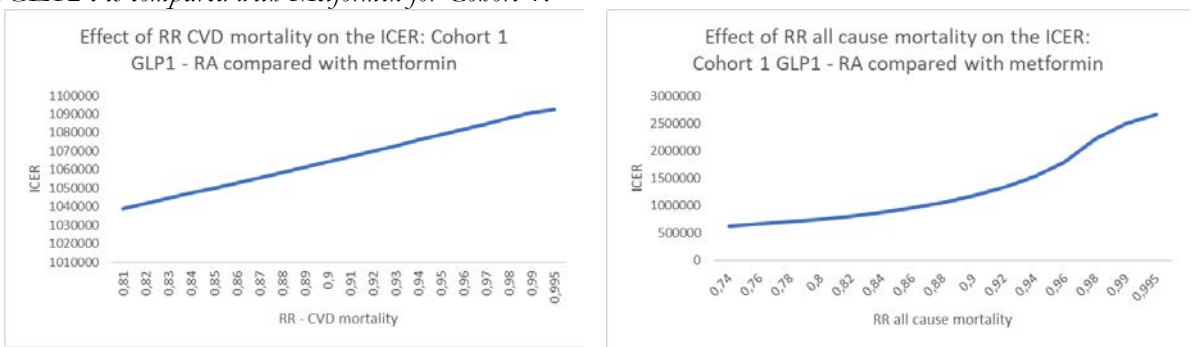

Figure 7: The effect of the RR risk of CVD mortality and all cause mortality of GLP1 – RA on the ICER, when GLP1-RA is compared with metformin for Cohort 1.

In Figure 6 and 7, the effect of the RR for CVD mortality and RR for all cause mortality on the ICER has been displayed. In Figure 6, SGLT2 i are reported compared to metformin.

Probabilistic sensitivity analysis (PSA)

To account for all uncertainty simultaneously, we have performed sensitivity analyses. Figure 8 to 10 represent the results for Cohort 1. In Figure 8 we see that the three scatterplots for each of

the interventions. The scatterplot for GLP-1 RA is above the two others, indicating higher costs than for SGLT-2 i. In Figure 9 and 10, the three alternative treatments are presented according to the threshold value. There we see that at a threshold of about NOK 110,000, SGLT-2 I are more likely to be cost-effective compared to metformin. From Figure 6 we have only reported with a frontier (the preferred alternative for each threshold value) the relevant alternatives, metformin and SGLT-2 i. For threshold values above NOK 110,000, SGLT-2 I is the preferred alternative. For a threshold value at NOK 250,000, SGLT-2 i is nearly 100% likely to be cost-effective.

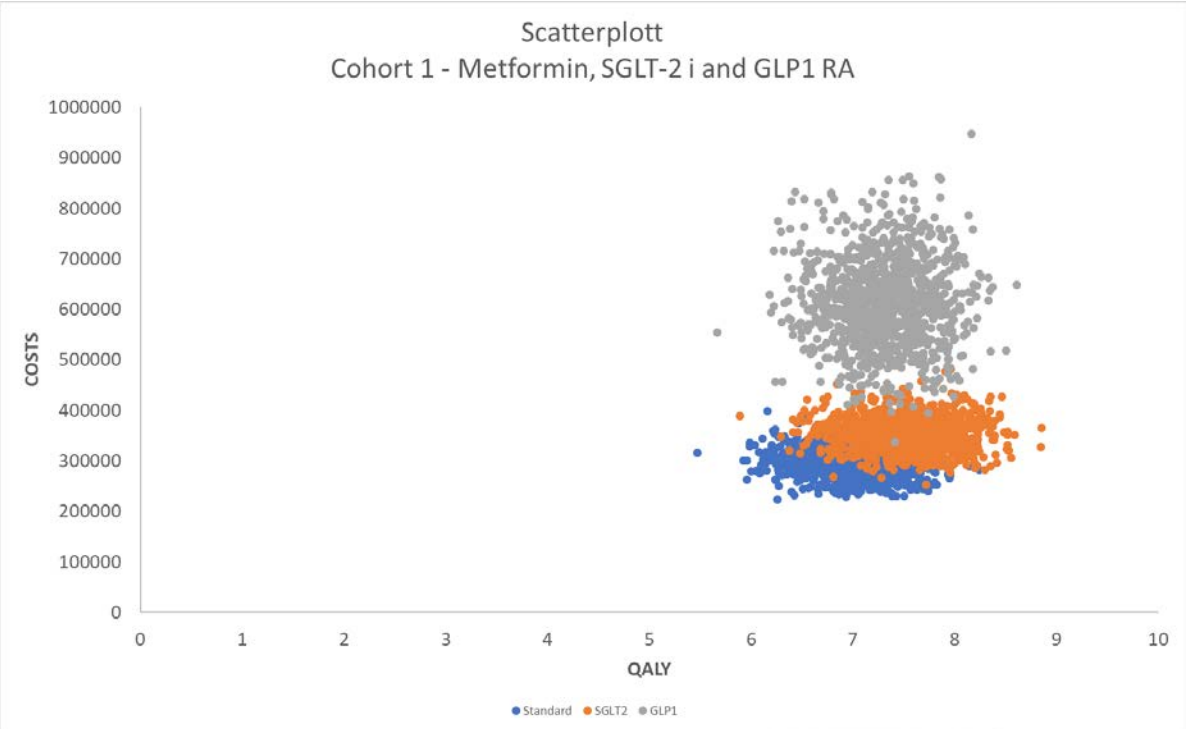

Figure 8: Scatter plot of QALYs and costs for metformin, SGLT-2 i and GLP-1 RA for Cohort 1

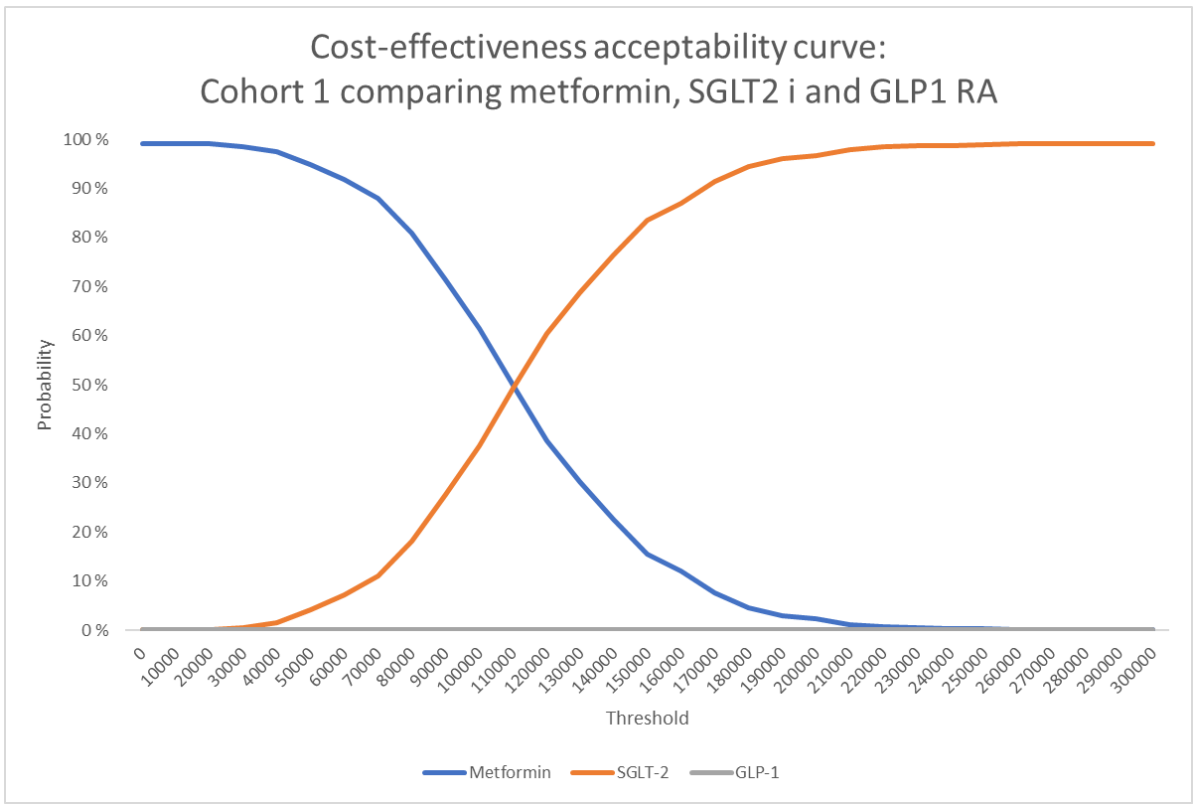

Figure 9: CEAC for metformin, SGLT-2 i and GLP-1 RA according to threshold values for Cohort 1

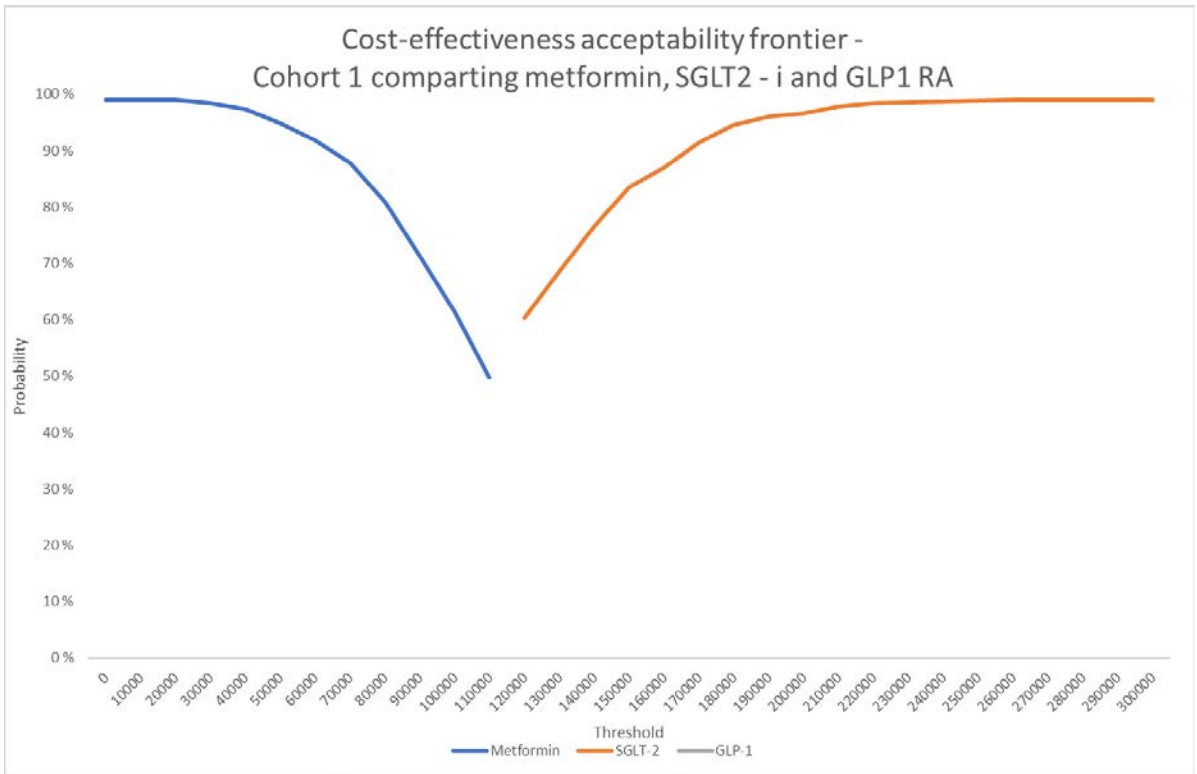

Figure 10: CEAF - for metformin, SGLT-2 i and GLP-1 RA. GLP-1 RA is not visible as SGLT-2 i is a dominating alternative. Cohort 1

The result of the PSA for Cohort 2 is presented in Table 11 and 12. The scatterplots indicate that SGLT-2 i result in higher QALYs, but with a substantial variation in costs. From Figure 8 we report the likelihood for SGLT-2 i to be a cost-effective alternative compared to metformin according to increasing threshold values. We see that above NOK 150,000, SGLT-2 i has a higher probability of being cost-effective compared to metformin. Whether SGLT-2 i should be recommended, depends on the threshold value for Cohort 2. For a threshold value of NOK 660000, SGLT-2 i is 93% likely to be cost-effective.

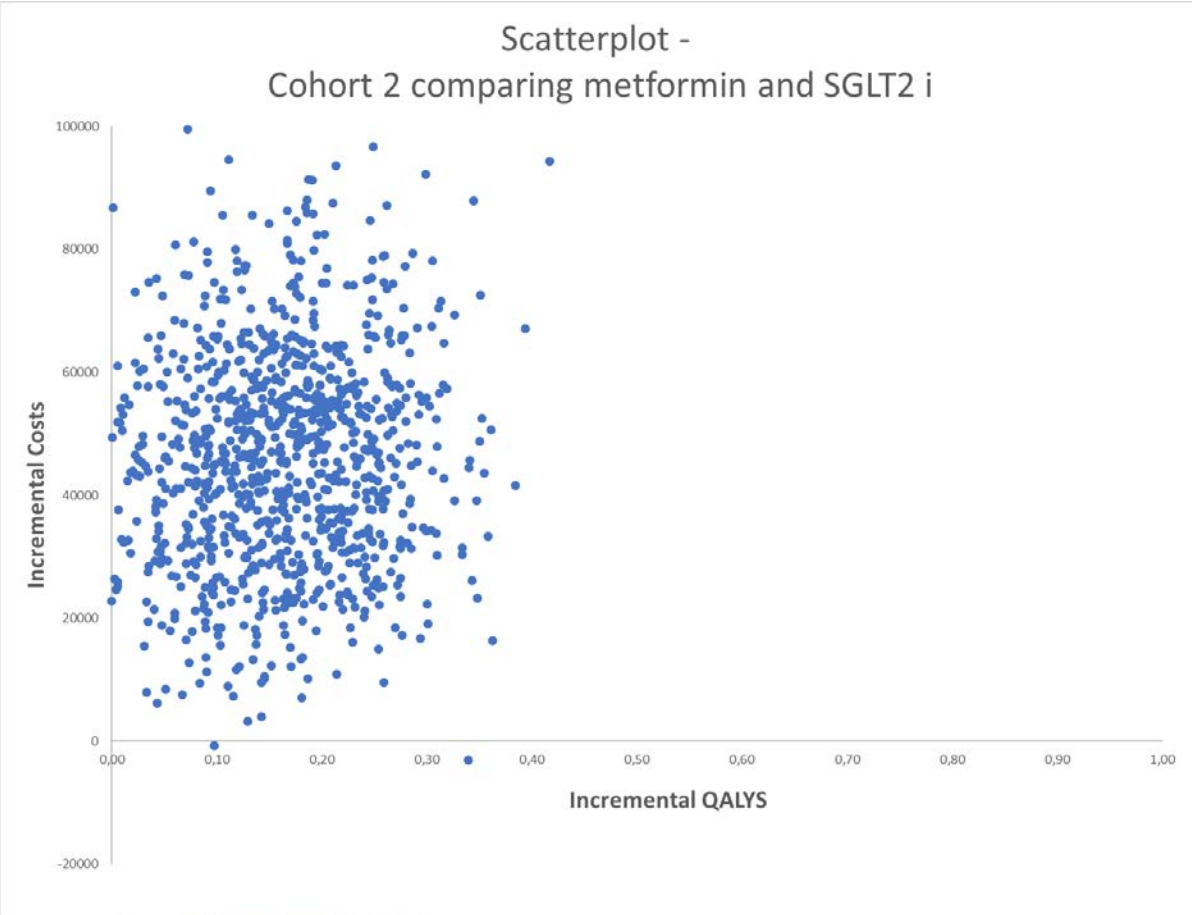

Figure 11: Scatter plot of QALYs and costs for metformin and SGLT-2 i for Cohort 2.

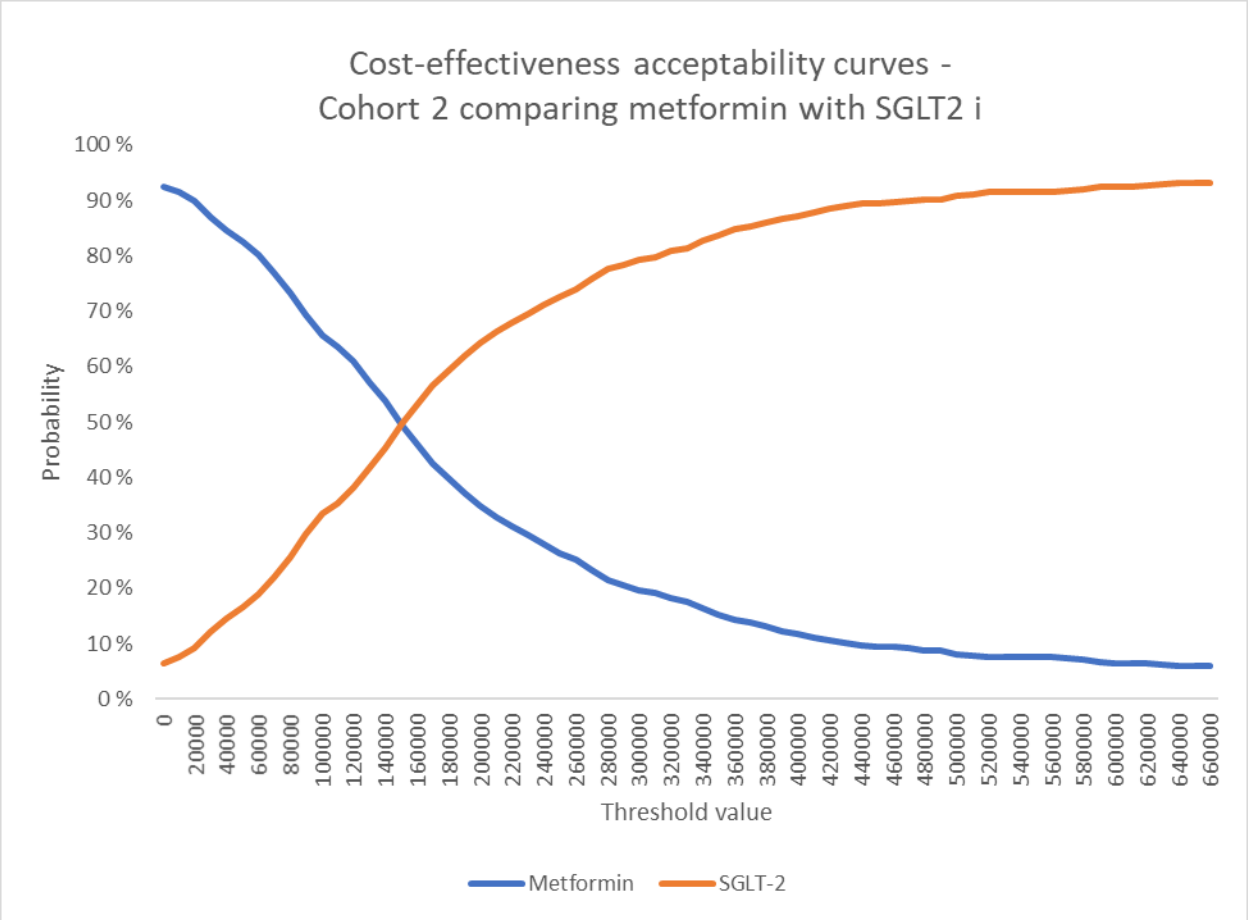

Figure 12: CEAC for metformin and SGLT-2 i for Cohort 2 according to threshold values

Validation

To validate the model, we have compared the 5 years output (MI, Stroke, heart failure, end-stage-kidney, all-cause mortality and CV mortality together with number of complications) from the model with the external 5 years health output as collected from the meta-analysis for SGLT-2 i and GLP-1 RA. Generally we see from Table 17-19 that there is a fairly good fit between the model predictions and the external numbers.

Table 17: Comparing SGLT-2 – RR in the model compared to data inputs – COHORT 1

Type	Model 5 years	External 5 years
Post MI	**0.88**	**0.87**
Heart failure	**0.728**	**0.700**
End Stage Kidney	**0.69**	**0.71**
All cause	**0.778**	**0.770**
CV mortality	**0.803**	**0.840**
Hypoglycemia	**0.90**	**0.90**
Genital Infection	**3.47**	**3.50**
GI events	**0.94**	**1.00**
Microvascular	**0.881**	**0.910**
Ketoacidosis	**1.04**	**1.04**
Amputations	**1.108**	**1.100**
AKI	**0.614**	**0.750**

Table 18: Comparing GLP1 – RA – RR in the mocel compared with data inputs – COHORT 1

Type	**Model 5 years**	**External 5 years**
Post MI	**0.91**	**0.92**
Stroke	**0.86**	**0.84**
Heart failure	**0.955**	**0.94**
End Stage Kidney	**0.79**	**0.78**
All cause	**0.876**	**0.88**
CV mortality	**0.778**	**0.88**
Hypoglycemia	**0.90**	**0.90**
Genital Infection	**0.70**	**0.70**
GI events	**2.04**	**2.46**
Microvascular	**1.127**	**1.180**
Ketoacidosis	**0.50**	**0.50**
Amputations	**0.330**	**0.330**
AKI	**0.834**	**0.860**

Table 19: Comparing SGLT2 i – RR in the model compared to data inputs – COHORT 2

Type	5-year (model)	5- year (External)
Post ESKD	**0.75**	**0.71**
Heart Failure	**0.53**	**0.70**
CV mortality	**0.73**	**0.84**
All cause mortality	**0.86**	**0.77**
Hypoglycemia	**0.90**	**0.90**
Genital infection	**3.51**	**3.51**
GI events	**1.00**	**1.00**
Microvascular	**0.92**	**0.91**
Ketoacidosis	**1.04**	**1.04**
Amputation	**1.11**	**1.10**
AKI	**0.75**	**0.75**

Scenario analyses

No discounting

From Table 20 and 21 we see that the effect of not discounting the LY and QALYs resulted in a reduction in the ICER as the incremental health benefit increased substantially in Cohort 1, while the incremental effects in Cohort 2 declined slightly.

Table 20: Discounted Costs, not discounted LY and QALYs - ICER for Cohort 1 (T2DM with established CV disease). Numbers in NOK

Intervention	Costs	Incr. Costs	Life Years	QALY	Incr. LY	Incr. QALY	ICER-LY(next lowest cost)	ICER-QALYs	ICER LY (metaf.)	ICER - QALYs (metaf.)
Metformin	291,356		16,13	10.05						
SGLT-2	338,588	47,232	17,67	11.06	1.54	1.01	30,670	46,764	30,670	46,764
GLP-1	608,268	269,680	16,92	10.60	-0.75	-0.46	(domin.)	(domin.)	205,787*	313,774

*The ICER is given by (632,517-296,550)/(16,883-16,128)

Table 21: Discounted Costs, not discounted LY and QALYs - ICER Cohort 2 (T2DM with renal and/or HF). Numbers in NOK

Intervention	Costs	Incr. Costs	Life Years	QALY	Incr. LY	Incr. QALYs	ICER-LY	ICER-QALYs
Metformin	258,527		14.83	8.78				
SGLT-2	282,746	24,219	14.95	8.96	0.12	0.18	201,825	134,550

5.3 Budget Impact Analysis (BIA)

Based on the Results in 4.1, we estimated the budget impact for SGTL-2 *i,* only, as GLP-2 RA was not a cost-effective treatment alternative for Cohort 1. SGTL-2 *i* is a cost-effective strategy for both Cohort 1 and 2. We do not assume that the use of GLP-1 RA, DPP-4 i and SU will be influenced by an increase in SGTL-2 *i*. The use of GLP-1 RA is expected to increase in the next years, but not due to an increase in the use of SGLT-2 i.

Table 22: Number of individuals with T2DM, individuals in Cohort 1, Cohort 2 and Cohort 1 and 2 together accounting for overlap. Number of individual expected to be treated over the next 5 years with a 3% annual increase.

	Number of patients in each cohort according to cohort				
	Year 1	Year 2	Year 3	Year 4	Year 5
T2DM	220 000	226 600	233 398	240 400	247 612
T2DM+CVD (Cohort 1)	54 120	55 744	57 416	59 138	60 913
T2DM+CKD (Cohort 2)	35 860	36 936	38 044	39 185	40 361
T2DM + CVD and/or CKD	65 780	67 753	69 786	71 880	74 036

Table 23: Number of current users of SGLT-2 i the next 5 years in Cohort 1, Cohort 2 and Cohorts combined according to two levels of current users.

	Number of patients according to assumption of current and future use in Cohort 1				
	Year 1	Year 2	Year 3	Year 4	Year 5
T2DM	37 639	38 768	39 931	41 129	42 363
Cohort 1 - 30%	16 236*	16 723	17 225	17 742	18 274
Cohort 1 – 50%	27 060	27 872	28 708	29 569	30 456
Cohort 2 - 30%	10 758*	11 081	11 413	11 756	12 108
Cohort 2 - 50%	17 930	18 468	19 022	19 593	20 180
Cohorts combined – 30%	19 734	20 326	20 936	21 564	22 211
Cohorts combined – 50%	32 890	33 877	34 893	35 940	37 018

**As an example, the number 16236 (Cohort 1 – 30%) is calculated by 30% of the number of individuals in Cohort 1 (54120*0.3), while 10758 for Cohort 2 is calculated taking 30% of Cohort 2 (35860*0.3). All numbers are based on Table 22.*

The number of individuals in Cohort 1, Cohort 2 and the Combined cohort 1 and 2 are presented in Table 22, assuming a 11% overlap between the cohorts. In Table 23 we have presented the estimated numbers of current users of SGLT-2 *i* in Cohort 1 and 2. The numbers were based on expert opinion (Kåre Birkeland and Tore Julsrud Berg). We assumed that the proportion of current users of SGLT-2 i were between 30% and 50%. The suggested compliance rate with reimbursement were assumed to be about 75%. To account for uncertainty, we also

included 70% and 80% compliance (Table 24). Lastly, we also included one alternative where the implementation to full compliance increased gradually.

Table 24: Number of users of SGLT-2 i in Cohort 1, Cohort 2 and cohorts combined the next 5 years if SGLT-2 i is reimbursed according to rates of compliance.

	Number of patients according to years, compliance and Cohort				
	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort 1 - 70%	37 884	39 021	40 191	41 397	42 639
Cohort 1 - 75%	40 590	41 808	43 062	44 354	45 684
Cohort 1 - 80%	43 296	44 595	45 933	47 311	48 730
Cohort 2 - 70%	25 102	25 855	26 631	27 430	28 253
Cohort 2 - 75%	26 895	27 702	28 533	29 389	30 271
Cohort 2 - 80%	28 688	29 549	30 435	31 348	32 289
Cohorts combined - 70%	46 046	47 427	48 850	50 316	51 825
Cohorts combined - 75%	49 335	50 815	52 340	53 910	55 527
Cohorts combined - 80%	52 624	54 203	55 829	57 504	59 229

The budget impact are presented in Tables 25 to 30. In Tables 25-27, the budget impact for Cohort 1 is presented. The budget impact in sensitive to the proportion of current users and compliance. In Table 25 we have assumed 75% compliance with reimbursement and 50% current users. The average yearly budget impact over five years will be about NOK125 million. With a gradual increase in compliance from the current 50% to 75% (Table 26), the average yearly budget impact will be about NOK 97 million. In Table 27 we have estimated the yearly budget impact for 70% compliance and 50% current users resulting in NOK 100 million. The budget impact is sensitive to the proportion of current users and compliance to SGLT-2 *i*.

For Cohort 2, the yearly budget impact was NOK83 million when assuming 75% compliance and 50% of current users (Table 28). Reducing the proportion of current users to 30%, increased the yearly budget impact to NOK150 million (Table 29).

There is a substantial overlap between the two cohorts, therefor we also estimated the budget impact for the two cohorts combined (Table 30). We see from Table 30, that the yearly budget impact was NOK 150 million, which was less than the sum of the yearly budget impact in Table 25 and 28.

Table 25: Budget impact of reimbursement of SGLT-2 i to Cohort 1, assuming 75% compliance from year 1 and 50% of current users in Cohort 1. Numbers in NOK and with VAT

BIA - Cohort 1	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Y1 – w/reimbursement (75%)	354 655 125	365 294 779	376 253 622	387 541 231	399 167 468	376 582 445
Y2 - no reimbursement (50%)	236 436 750	243 529 853	250 835 748	258 360 821	266 111 645	251 054 963
BIA (Y1 - Y2)	118 218 375	121 764 926	125 417 874	129 180 410	133 055 823	125 527 482

Table 26: Budget impact of reimbursement of SGLT-2 i to Cohort 1, assuming 75% compliance from year 1 and 50% of current users in Cohort 1 with gradually increase in compliance (60% in Year 1, 65% in Year 2, 70% in Year 3 and 75% in Year 4 and 5. Numbers in NOK and with VAT

BIA - Cohort 1	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Y1 - with reimbursement (75%)	283 724 100	316 588 808	351 170 047	387 541 231	399 167 468	347 638 331
Y2 - no reimbursement (50%)	236 436 750	243 529 853	250 835 748	258 360 821	266 111 645	251 054 963
BIA (Y1 - Y2)	47 287 350	73 058 956	100 334 299	129 180 410	133 055 823	96 583 368

Table 27: Budget impact of reimbursement of SGLT-2 i to Cohort 1, assuming 70% compliance and 50% of current users in Cohort 1. Numbers in NOK and with VAT

BIA - Cohort 1	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Y1 - with reimbursement (70%)	331 011 450	340 941 794	351 170 047	361 705 149	372 556 303	351 476 949
Y2 - no reimbursement (50%)	236 436 750	243 529 853	250 835 748	258 360 821	266 111 645	251 054 963
BIA (Y1 - Y2)	94 574 700	97 411 941	100 334 299	103 344 328	106 444 658	100 421 985

Table 28: Budget impact of reimbursement of SGLT-2 i to Cohort 2, assuming 75% compliance and 50% of current users in Cohort 2. Numbers in NOK and with VAT

BIA - Cohort 2	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Y1 - with reimbursement (75%)	234 995 063	242 044 914	249 306 262	256 785 450	264 489 013	249 524 140
Y2 - no reimbursement (50%)	156 663 375	161 363 276	166 204 175	171 190 300	176 326 009	166 349 427
BIA (Y1 - Y2)	78 331 688	80 681 638	83 102 087	85 595 150	88 163 004	83 174 713

Table 29: Budget impact of reimbursement of SGLT-2 i to Cohort 2, assuming 75% compliance and 30% of current users in Cohort 2. Numbers in NOK and with VAT

BIA - Cohort 2	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Y1 - with reimbursement (75%)	234 995 063	242 044 914	249 306 262	256 785 450	264 489 013	249 524 140
Y2 - no reimbursement (30%)	93 998 025	96 817 966	99 722 505	102 714 180	105 795 605	99 809 656
BIA (Y1 - Y2)	140 997 038	145 226 949	149 583 757	154 071 270	158 693 408	149 714 484

Table 30: Budget impact of reimbursement of SGLT-2 i to the Cohorts combined, assuming 75% compliance and 50% of current users when considering both cohorts. Numbers in NOK and with VAT

BIA - Cohorts Combined	Year 1	Year 2	Year 3	Year 4	Year 5	Average
Y1 - with reimbursement (75%)	431 064 563	443 996 499	457 316 394	471 035 886	485 166 963	457 716 061
Y2 - no reimbursement (50%)	287 376 375	295 997 666	304 877 596	314 023 924	323 444 642	305 144 041
BIA (Y1 - Y2)	143 688 188	147 998 833	152 438 798	157 011 962	161 722 321	152 572 020

Table 31: Budget impact of reimbursement of SGLT-2 i on other costs in the health care sector for Cohort 1. Numbers in NOK (without VAT)

Cohort 1	Year 1	Year 2	Year 3	Year 4	Year 5
SGLT-2 i	496 496 880	567 079 643	622 216 195	685 473 023	752 696 217
Standard of care (Metformin)	514 735 320	593 613 596	653 335 617	723 972 112	801 121 684
Budget impact on health care	-18 238 440	-26 533 954	-31 119 422	-38 499 089	-48 425 467

Table 32: Budget impact of reimbursement of SGLT-2 i on other costs in the health care sector for Cohort 2. Numbers in NOK (without VAT)

Cohort 2	Year 1	Year 2	Year 3	Year 4	Year 5
SGLT-2 i	702 031 220	692 583 186	681 974 485	691 109 200	698 927 037
Standard of care (Metformin)	747 645 140	728 964 949	708 909 548	721 125 056	732 305 374
Budget impact on health care	-45 613 920	-36 381 763	-26 935 063	-30 015 856	-33 378 337

The consequences for the health care sector, not including the drugs, are presented in Table 31 and 32 for Cohort 1 and 2, respectively. As SGLT-2 *i* are expected to reduce both cardiovascular and kidney events, the costs are expected to decline. The majority of the costs are in specialist care, related to treatment of MI, HF, stroke and kidney disease.

The total budget impact of financing SGLT-2 *i*, would therefore be a combination of the additional cost on National Insurance Scheme and the cost-savings in the health care sector.

6. Discussion

The cost-effectiveness analyses indicate that SGLT-2 i is a cost-effective alternative for individuals with T2DM and established CVD. Compared to metformin as first line treatment, SGLT-2 i in addition to metformin resulted in an ICER of NOK 123,205 per QALY gained. SGLT-2 i was a dominating strategy, compared to GLP-1 RA with lower incremental effect than SGLT-2 i and more costly. When comparing GLP-1 RA to metformin, the ICER was NOK 1.2 mill per QALY gained. In the probability sensitivity analysis for Cohort 1, GLP-1 RA was not at the frontier, and would never be the preferred treatment option (CEAF), while SGLT-2 i is the preferred option for threshold values above NOK 123,000. The likelihood for SGLT-2 i to be cost effective is 99% for threshold values of NOK 300,000.

The cost-effectiveness of SGLT-2 i for individuals with T2DM and established CKD was about NOK 194,000 per QALY gained. The incremental health gain costs were positive, hence all simulations in the PSA resulted in simulated ICERs in the upper right quadrant in the cost-effectiveness plane. For threshold values above NOK 194,000, SGLT-2 i was the preferred alternative. For a threshold value of NOK 660,000, the likelihood for SGLT-2 i to be cost-effective was above 93%. The likelihood will continue to increase with increased threshold values.

The analyses in this report is for patients with T2DM with either established CVD (Cohort 1) or CKD (Cohort 2). To evaluate the cost-effectiveness of new treatment options for these two cohorts, the clinical pathway for the comparator, standard of care has to be described and modelled within the framework of mathematical simulation models. Even though there is a substantial literature on T2DM and the clinical pathway, it is still challenging to have separate estimates for some of the transitions, such as the risk of second MI for an individual with T2DM with established CVD and experienced a stroke or the risk of stroke for an individual with T2DM with established CVD who has experienced an MI. For several of these transitions, we have combined the risks additive, but the combined risk of several events, could be both higher (due to increased severity),

or lower as they could be partly overlapping. In the future, more research is needed to understand the marginal effect of additional events.

In this study, the aim was to estimate the cost-effectiveness of groups of drugs, either SGLT-2 i or GLP-1 RA. We know from the clinical studies, that the drugs have different clinical effects and adverse events. Therefore, in addition to the more aggregate analysis conducted in this report, there might be a need for some additional recommendations with regard to each drug, both with regard to efficacy, adverse events and price of the drug.

The treatment recommendations from European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD), recommend to SGLT-2 i and GLP-1 RA as monotherapy, not in combination with metformin, which would have been the preferred analysis if the aim was to estimate the cost-effectiveness of the ESC and EASD recommendations. This analysis was not conducted due to the fact that there are not sufficient evidence on cardiovascular and renal outcomes and mortality to evaluate the efficacy. In the future you could consider having several strategies, both the ESC and EASD recommendation, the current evaluation SGLT-2 i and GLP-1 RA in combination with metformin compared to standard of care.

In the current model we have assumed that the individuals stay on life-long treatment with either SGLT-2 i or GLP-1 RA, and that the efficacy remains over the life course. There might be reasons to believe that some individuals would, for different reasons, have to switch medication. Further, the efficacy of the drug is in Li et al 2021 and Palmer et al 2020 are provided for 5 years, which we have extrapolated. There might be reasons that the efficacy would be reduced over the years, which would result in a lower ICER (given that the individuals still use the drugs). There might be a reduction in the compliance. In the studies, there might be a lower compliance than 100%. As we have assumed 100% compliance, this could have resulted in an overestimation of the costs.

For the analysis, we have applied drug prices as published in "Felleskatalogen". In reality, there will be negotiations and the prices are likely to decline. In the deterministic sensitivity analysis we explored the effect of lower (and higher) price on SGLT-2 i and GLP-1 RA on the ICER. For Cohort 1, we saw that a reduction in the price of SGLT-1 i to NOK2000 resulted in that SGLT-2 I was a cost saving alternative to metformin, while an increase to NOK9000 increased the ICER to about NOK120,000. A reduction in the price of GLP-1 RA to NOK20,000 reduced the ICER

to around NOK550,000. Similar as for Cohort 1, a reduction in the price of SGLT-1 resulted in SGLT-1 i being a cost-saving alternative to metformin.

The analyses are based on a large number of clinical trials with moderate to high quality, where the studies are mainly RCTs. There are continuously updates on the recommendations of the evidence.

With regard to the budget impact, the consequences depend on the number of current users of SGLT-2 *i* in the two Cohorts and compliance. Financing SGLT-2 *i*, would reduce the costs in the health care sector, due to less events (MI, HF, kidney disease).

7. Conclusion

SGLT2 i is likely to be cost-effective in treatment of T2DM with established CVD and for patients with T2DM with CKD. SGLT-2 *i* dominates GLP-1 RA, as SGLT-2 *i* implies higher health benefits to higher incremental costs. The budget impact of introducing SGLT-2 *i* depends greatly on the use of the current use of SGLT-2 *i* in the two cohorts.

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Appendix

A1 Transition Probabilities

Table A1. Transition Probabilities for the Post MI health state

Health State	Post MI	Source
Transition probability		
Stay in Post MI	0.61	
MI event	0.1	Korman et al.,2016
Stroke wo sequel	0.0100	Korman et al.,2016
Stroke w/moderate sequel	0.0030	Korman et al.,2016
Stroke w/severe sequel	0.0011	Korman et al.,2016
HF event	0.09	Swedeheart
All Stroke events	0.01	Birkeland et al.,2020
Adverse Events		
Hypoglycemia	0.10	EMPA.REG
Genital Infection	0.02	Palmer et al.,2020
Gastrointestinal event	0.01	Palmer et al.,2020
Diabetes Complications		
Microvascular complications	0.05	Birkeland et al.,2020
Ketoacidosis	0.0004	Palmer et al.,2020
Amputation	0.01	Slåtsve et al.,2020
Post Event		
Return to Post MI after MI event	0.86	
Death from MI the first year	0.14	Martine, 2019
Return to Post Stroke wo sequeI after stroke wo sequel	0.97	
Death from stroke wo sequel event the first year	0.03	SSB Life Tables, 2021
Return to Post Stroke w/mod. sequeI after stroke w/mod. sequel	0.93	
Death from stroke w/mod. sequel event the first year	0.07	SSB Life Tables, 2021
Return to Post Stroke w/severe sequeI after stroke severe sequel	0.90	
Death from stroke w/severe sequel event the first year	0.10	SSB Life Tables, 2021
Return to Post MI after hypoglyceima event	0.98	
Death from Hypoglycemia	0.02	Zoungas, 2010

Return to Post MI after genital infection event	0.97	
Death from genital infection event	0.03	Baena Díez et al., 2016
Return to Post MI after gastrointestinal event	0.91	
Death from gastrointestinal event	0.09	Baena Díez et al., 2016
Return to Post MI after microvascular complication	0.92	
Death from microvascular complication	0.08	Baena Díez et al., 2016
Return to Post MI after ketoacidosis event	0.998	
Death from ketoacidosis event	0.002	Medscape, 2021 *
Return to Post MI after an amputation	0.89	
Death from an amputation	0.11	Moulik et al.,1998

Table A2: Transition Probabilities for the Post Stroke without Sequelae health state

Health State	Post Stroke without sequel	Source
Transition probability		
Stay	0.65	
MI event	0.09	Korman et al.,2016
HF event	0.05	Swedeheart Study
Stroke recurrence	0.02	Korman et al.,2016
Adverse Events		
Hypoglycemia	0.10	EMPA.REG
Genital Infection	0.02	Palmer et al.,2020
Gastrointestinal event	0.01	Palmer et al.,2020
Diabetes Complications		
Microvascular complications	0.06	Birkeland et al.,2020
Ketoacidosis	0.00	Palmer et al.,2020
Amputation	0.01	Slåtsve et al.,2020
Other Events		
Return to Post Stroke wo sequel after MI event	0.83	
Death from MI the first year	0.17	Post MI health state probabilities: Death from MI the first year + Death from stroke wo sequel event the first year
Return to Post Stroke wo sequel after stroke wo sequel event	0.87	
Death from stroke wo sequel the first year	0.13	Probability of dying from stroke wo sequel combined with the relative risk of dying from stroke
Return to Post Stroke wo sequel after hypoglyceima event	0.98	
Death from Hypoglycemia	0.02	Zoungas, 2010
Return to Post Stroke wo sequel after genital infection event	0.97	
Death from genital infection event	0.03	Baena Díez et al., 2016
Return to Post Stroke wo sequel after gastrointestinal event	0.92	
Death from gastrointestinal event	0.08	Baena Díez et al., 2016
Return to Post Stroke wo sequel after microvascular complication	0.92	
Death from microvascular complication	0.08	Baena Díez et al., 2016

Return to Post Stroke wo sequel after ketoacidosis event	0.998	
Death from ketoacidosis event	0.002	Medscape, 2021 *
Return to Post Stroke wo sequel after an amputation	0.89	
Death from an amputation	0.11	Moulik et al.,1998

Table A3: Transition Probabilities for the Post Stroke with Moderate Sequel health state

Health State	Post Stroke w/moderate sequel	Source
Transition probability		
Stay	0.67	
MI event	0.07	Korman et al.,2016
HF event	0.05	Swedeheart Study
Stroke recurrence	0.03	Korman et al.,2016
Adverse Events		
Hypoglycemia	0.10	EMPA.REG
Genital Infection	0.02	Palmer et al.,2020
Gastrointestinal event	0.01	Palmer et al.,2020
Diabetes Complications		
Microvascular complications	0.06	Birkeland et al.,2020
Ketoacidosis	0.00	Palmer et al.,2020
Amputation	0.01	Slåtsve et al.,2020
Other Events		
Return to Post Stroke moderate sequel after MI event	0.79	
Death from MI the first year	0.21	Post MI health state probabilities: Death from MI the first year + Death from stroke wo sequel event the first year
Return to Post Stroke moderate sequel after stroke wo sequel event	0.75	
Death from stroke moderate sequel the first year	0.25	Probability of dying from stroke w/moderate sequel combined with the relative risk of dying from stroke
Return to Post Stroke moderate sequel after hypoglyceim event	0.98	
Death from Hypoglycemia	0.02	Zoungas, 2010
Return to Post Stroke moderate sequel after genital infection event	0.97	
Death from genital infection event	0.03	Baena Díez et al., 2016
Return to Post Stroke moderate sequel after gastrointestinal event	0.92	
Death from gastrointestinal event	0.08	Baena Díez et al., 2016
Return to Post Stroke moderate sequel after microvascular complication	0.92	
Death from microvascular complication	0.08	Baena Díez et al., 2016
Return to Post Stroke moderate sequel after ketoacidosis event	1.00	

Death from ketoacidosis event	0.00	Medscape, 2021 *
Return to Post Stroke moderate sequel after an amputation	0.89	
Death from an amputation	0.11	Moulik et al.,1998

Table A4: Transition Probabilities for the Post Stroke with Severe Sequel health state

Health State	Post Stroke w/severe sequel	Source
Transition probability		
Stay	0.67	
MI event	0.07	Korman et al.,2016
HF event	0.05	Swedeheart Study
Stroke recurrence	0.03	Korman et al.,2016
Adverse Events		
Hypoglycemia	0.10	EMPA.REG
Genital Infection	0.02	Palmer et al.,2020
Gastrointestinal event	0.01	Palmer et al.,2020
Diabetes Complications		
Microvascular complications	0.06	Birkeland et al.,2020
Ketoacidosis	0.00	Palmer et al.,2020
Amputation	0.01	Slåtsve et al.,2020
Other Events		
Return to Post Stroke severe sequel after MI event	0.76	
Death from MI the first year	0.24	Post MI health state probabilities : Death from MI the first year + Death from stroke wo sequel event the first year
Return to Post Stroke severe sequel after stroke wo sequel event	0.64	
Death from stroke severe sequel the first year	0.36	Probability of dying from stroke severe sequel combined with the relative risk of dying from stroke
Return to Post Stroke severe sequel after hypoglyceima event	0.98	
Death from Hypoglycemia	0.02	Zoungas, 2010
Return to Post Stroke severe sequel after genital infection event	0.97	
Death from genital infection event	0.03	Baena Díez et al., 2016
Return to Post Stroke severe sequel after gastrointestinal event	0.92	
Death from gastrointestinal event	0.08	Baena Díez et al., 2016
Return to Post Stroke severe sequel after microvascular complication	0.92	
Death from microvascular complication	0.08	Baena Díez et al., 2016
Return to Post Stroke severe sequel after ketoacidosis event	1.00	
Death from ketoacidosis event	0.00	Medscape, 2021 *
Return to Post Stroke severe sequel after an amputation	0.89	
Death from an amputation	0.11	Moulik et al.,1998

A2: Data input Budget Impact Analysis

Information about the proportion of current use of T2DM drugs. This information was used to calculate number and proportion of patients on current treatment.

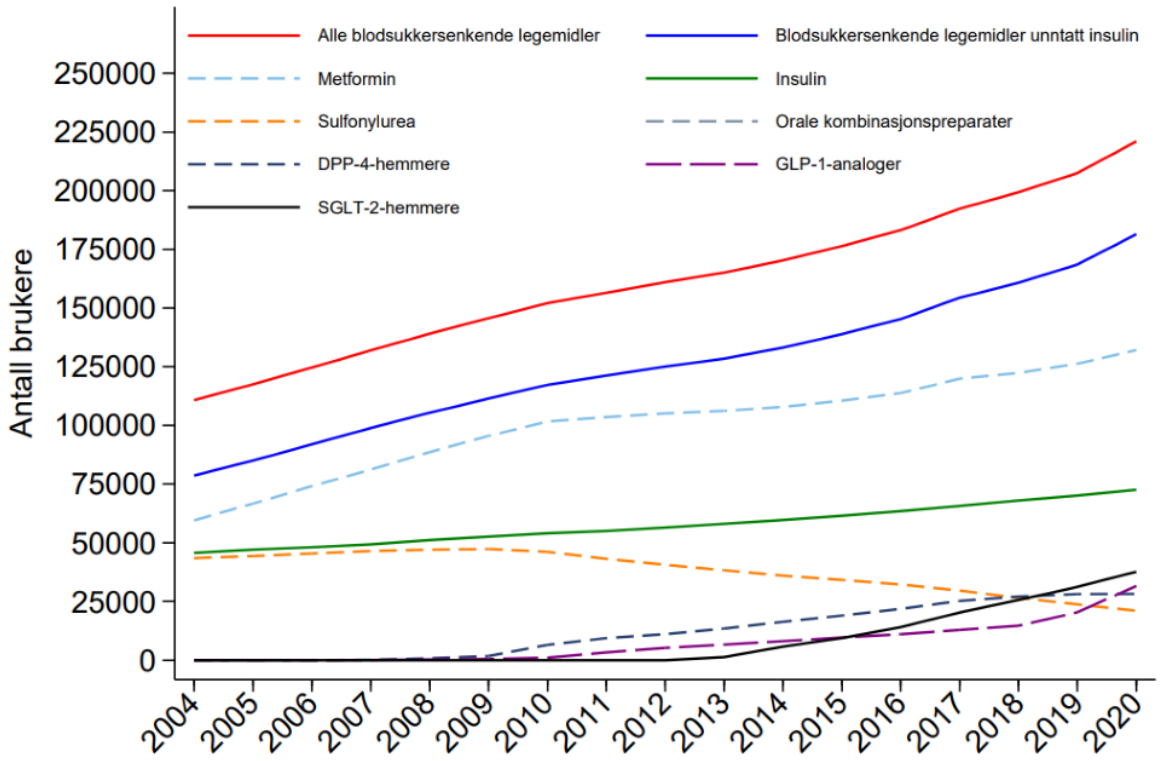

Figure A1: Number of users of T2DM related drugs.

A3: Markov Traces

In the following figures (A2 til A6), we have reported number of individuals in each health state according to age for a starting cohort of 1000 individuals. From all figures we see that the starting cohort is at 1000 when the individuals are 60, and that over the years the number of individuals dying is increasing and reaching almost 1000 individuals at the age of 90 years. For the other health states, they all peak at around 76-77 years. For cohort 1, we see that Post MI has the highest number of individuals, with HF being the second. For cohort 2, there are less health states.

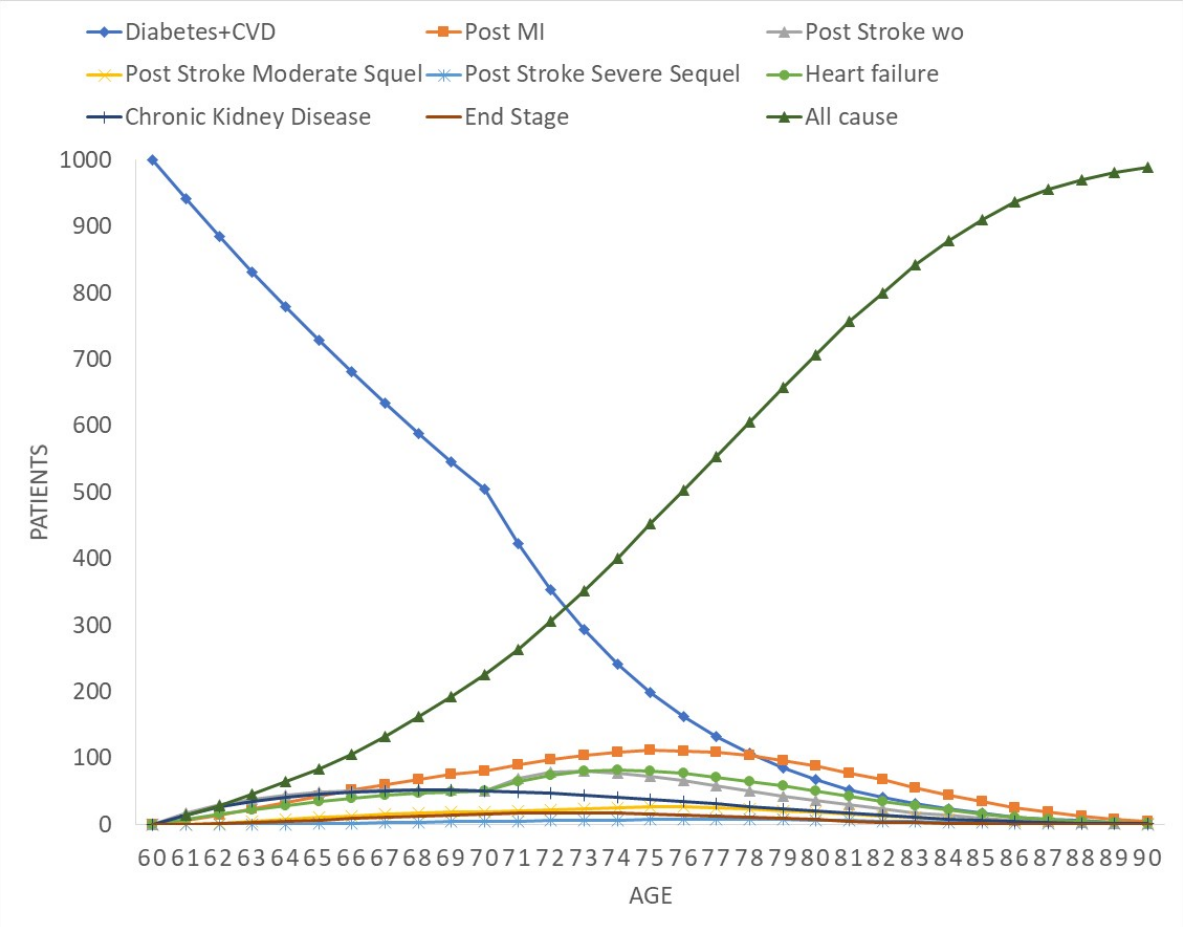

Figure A2: Markov traces for Cohort 1 – Metformin from the age of 60 years

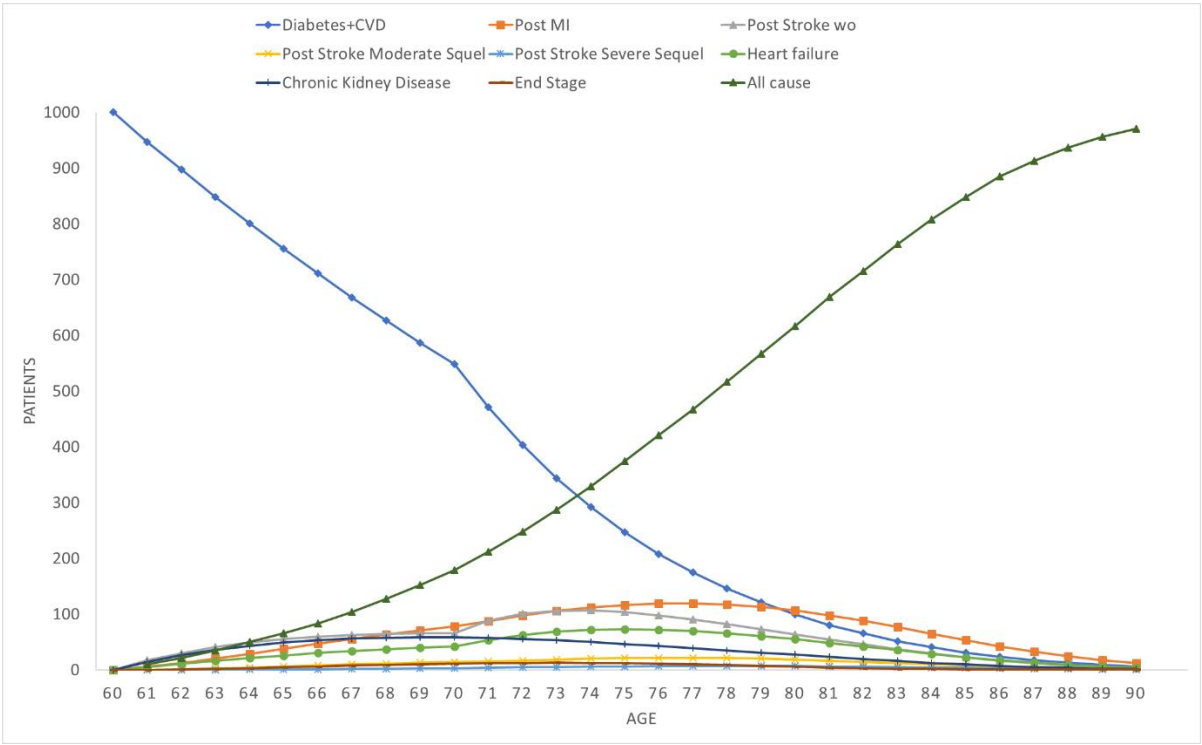

Figure A3: Markov traces for SGLT-2 *i* – number of patients in each health state according to age, Cohort 1

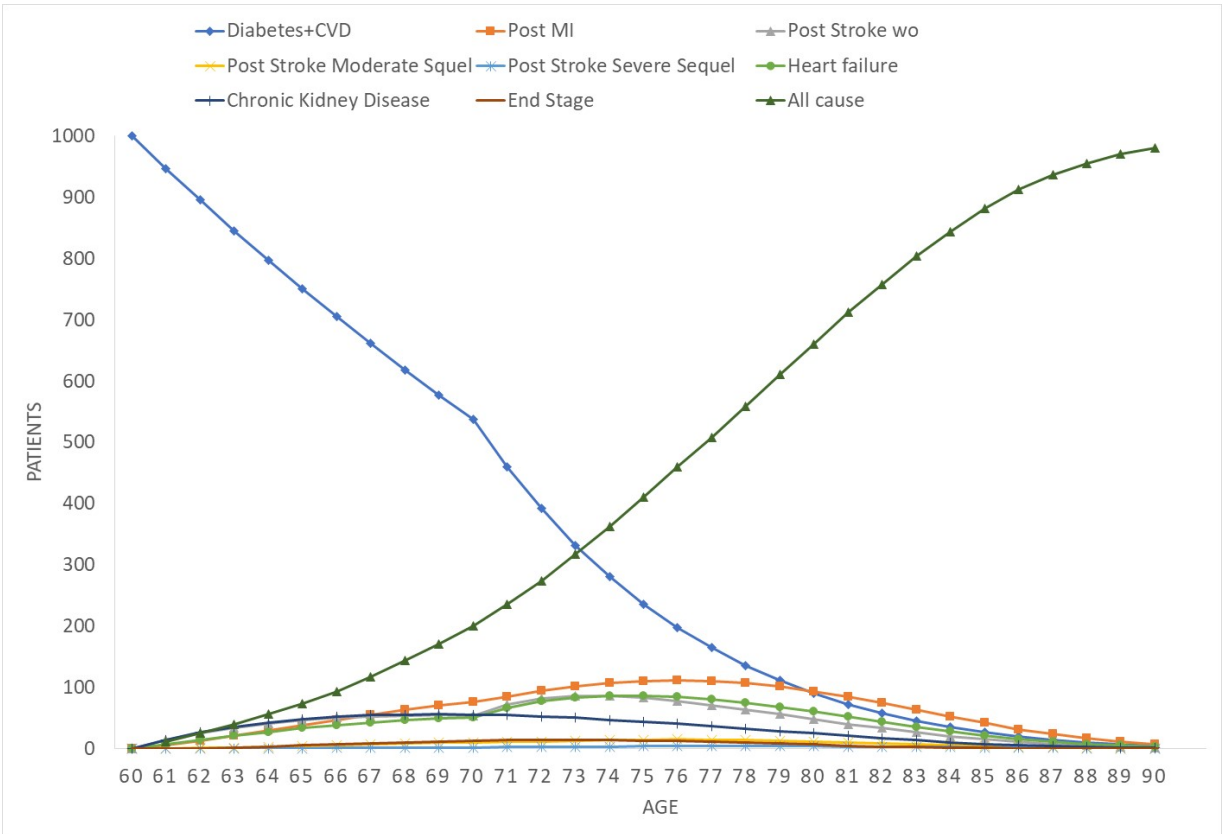

Figure A4: Markov traces for GLP-1 RA – number of patients in each health state according to age, Cohort 1

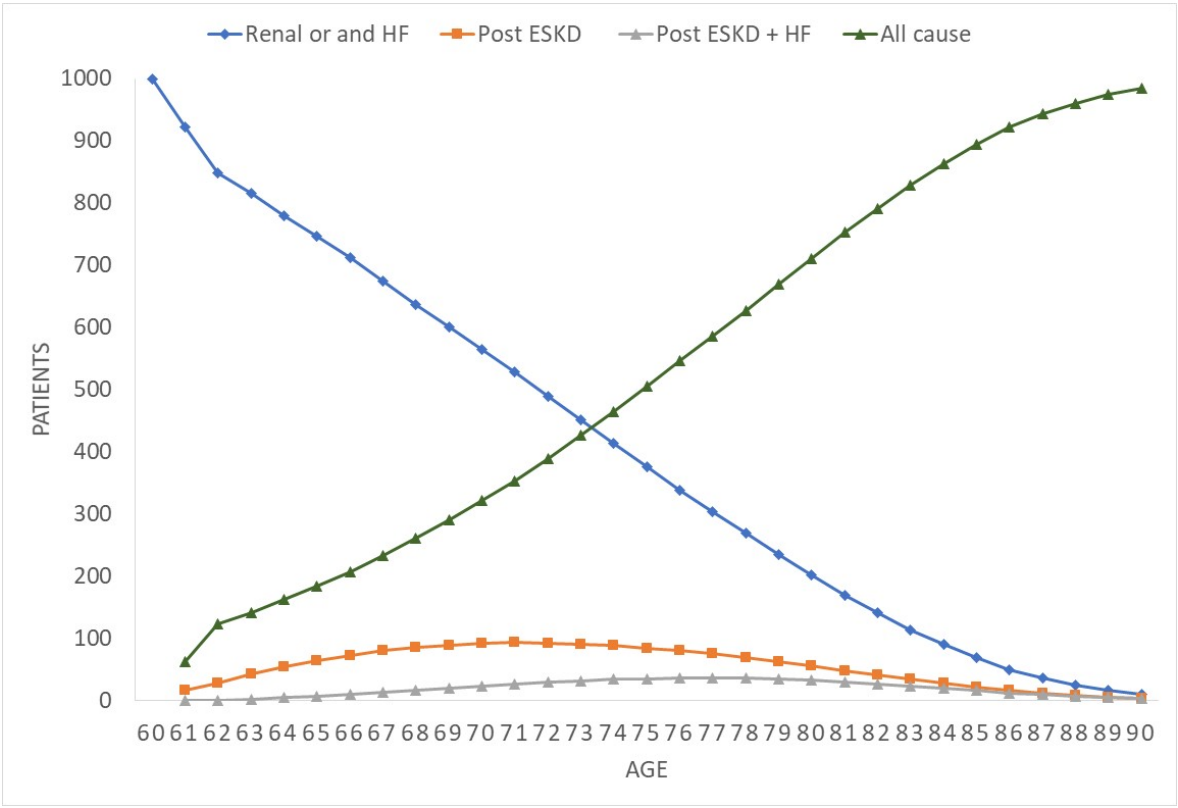

Figure A5: Markov traces for metformin – number of patients in each health state according to age, Cohort 2

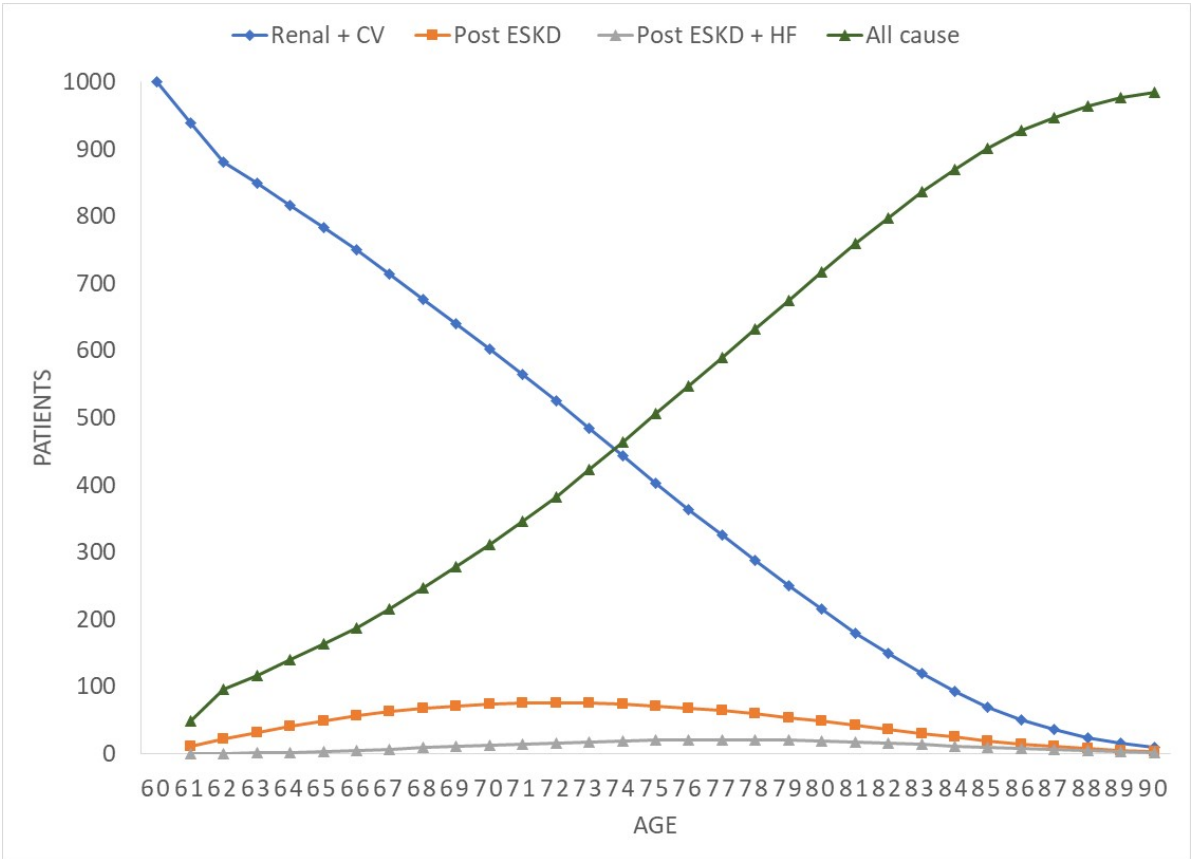

Figure A5: Markov traces for SGLT-2 – number of patients in each health state according to age, Cohort 2