THE COSTS OF DIABETES IN 2020 AND 2030

– A MODEL ANALYSIS COMPARING INNOVATIVE GLUCOSE LOWERING TREATMENTS IN SECOND LINE FOLLOWING EUROPEAN AND AMERICAN GUIDELINES COMPARED TO CURRENT STANDARD OF CARE

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Foreword

The disease burden for type 2 diabetes is shared by many - those who live with the disease, the health care system and the wider community in the form of production losses. In recent years, there has been a series of national initiatives to improve the diabetes care in Sweden and the National Guidelines for Diabetes Care were updated by the National Board of Health and Welfare (Socialstyrelsen) in February 2015. The national guidelines provide guidance regarding choices between treatment options at different stages of the disease.

The Swedish Institute for Health Economics (IHE) has previously demonstrated that a more intensive treatment strategy, in line with national guidelines, could reduce the disease burden in the form of diabetes-related mortality and diabetes complications, while being cost-neutral in 2030. That comparison was made between the current diabetes care and a more intensive approach with more frequent health care contacts together with additional glucose-lowering treatment and a lower threshold for treatment change.

During the past decade, new drugs with innovative modes of action, e.g. DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors, have been introduced for the treatment of type 2 diabetes. Clinical studies have demonstrated that these drug classes have improved risk control through reduced blood glucose, lower blood pressure and BMI and less hypoglycemia. There is, however, a discrepancy between European and US guidelines from the diabetes associations EASD/ADA and the Swedish guidelines regarding the use of these drugs as add-on options when metformin alone fails to achieve sufficient glucose control. While the international guidelines have included DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors as add-on options, the Swedish national guidelines still recommend NPH-insulin as first choice of add-on.

In this report, IHE estimate the long-term complications and societal costs of type 2 diabetes in 2020 and 2030 in Sweden, and the effects on complications, treatment costs and production losses from including DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors as add-on options to metformin in second-line treatment. The authors thankfully acknowledge Associate Professor Per Katzman, Department of Clinical Sciences, Lund University, who has been an adviser for this study. The study was funded by AstraZeneca.

Lund, October 2016

Ulf Persson
Managing Director at IHE

What is already known?

- The number of people living with type 2 diabetes in Sweden have been estimated to increase from around 421 000 individuals in 2013 to nearly 560 000 people in 2030, which would represent an increase of approximately 33 percent.
- The direct and indirect costs of type 2 diabetes in Sweden are high. The societal cost has previously been estimated to increase from about SEK 16 billion in 2013 to almost SEK 18 billion in 2020 and SEK 21 billion in 2030.
- A more intensive treatment strategy, with more frequent health care contacts and a lower threshold for treatment change, could reduce the disease burden in the form of diabetes-related mortality and diabetes complications while being cost-neutral in 2030.
- European and US guidelines from diabetes associations EASD/ADA have included DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors as add-on options when metformin alone fails to achieve sufficient glucose control.

What this report adds?

- The cumulative incidence of microvascular diabetes complications was estimated to decrease by 10 500 cases in year 2030 due to the use of DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors as add-on options to metformin, with almost 400 persons being spared from kidney failure and dialysis.

- The corresponding decrease for macrovascular complications was estimated to almost 9 000 cases in year 2030, with over 1 500 persons who avoid having myocardial infarction and almost 1 000 who avoid having a stroke.

- Further, the use of DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors was estimated to result in a higher survival rate which adds up to 6 389 life years gained during the period 2013 to 2030.

- At the current price level, the total societal cost was estimated to increase by SEK 503 million in 2030 due to the use DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors. The increase in costs of prevention was partially offset by decreases in costs of microvascular complications, macrovascular complications and by indirect costs.

- Accounting for expected price reduction of DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors due to patent expiry, the total societal cost was instead estimated to decrease by SEK 113 million in year 2030.

Executive summary in Swedish

Bakgrund

Det senaste decenniet har flera läkemedel med nya verkningsmekanismer introducerats i behandlingen av typ 2-diabetes. Bland dessa läkemedel kan nämnas DPP-4-hämmare, GLP-1-analoger och SGLT-2-hämmare. Kliniska studier har visat att dessa läkemedelsgrupper har förbättrad riskfaktorkontroll genom sänkt HbA1c-värde, lägre blodtryck och BMI samt färre hypoglykemier.

Typ 2-diabetes är en progressiv sjukdom där metformin vanligtvis är det första glukossänkande läkemedlet som används. Efterhand behövs tillägg av ytterligare glukossänkande läkemedel för att personer med typ 2-diabetes ska kunna nå målvärdena för glukoskontroll. Det råder samsyn om värdet av ett patientcentrerat och individanpassat arbetssätt för en framgångsrik diabetesvård. Socialstyrelsens nationella riktlinjer rekommenderar i första hand NPH-insulin som första tilläggsbehandling när målet för blodglukosnivån inte längre kan nås med enbart metformin. De nyare läkemedlen kan också användas men ges en lägre prioritet. Internationella rekommendationer från de amerikanska och europeiska diabetesorganisationerna EASD/ADA betonar behovet av individualiserade mål för glukossänkande behandling där patientens och läkemedlets egenskaper balanseras med målet att uppnå glukoskontroll samtidigt som bieffekter såsom hypoglykemi och viktuppgång minimeras. Rekommendationer från EASD/ADA inkluderar DPP-4-hämmare, GLP-1-analoger och SGLT-2-hämmare i andra linjens behandling efter metformin.

Syfte

Denna modellbaserade studie syftar till att skatta totala komplikationer och samhällskostnaden för typ 2-diabetes år 2020 och 2030 till följd av en behandlingsstrategi med DPP-4-hämmare, GLP-1-analoger eller SGLT-2-hämmare som tillägg till metformin jämfört med en vård som omfattar sulfonureider eller NPH-insulin som tillägg till metformin.

Metod

IHE:s kohortmodell för typ 2-diabetes användes för att beräkna kostnader för personer med typ 2-diabetes i Sverige i framtiden. För att ta hänsyn till att demografiska och kliniska egenskaper påverkar kostnader för typ 2-diabetes skapades kohorter utifrån publicerade studier och statistik från Nationella diabetesregistret (NDR).

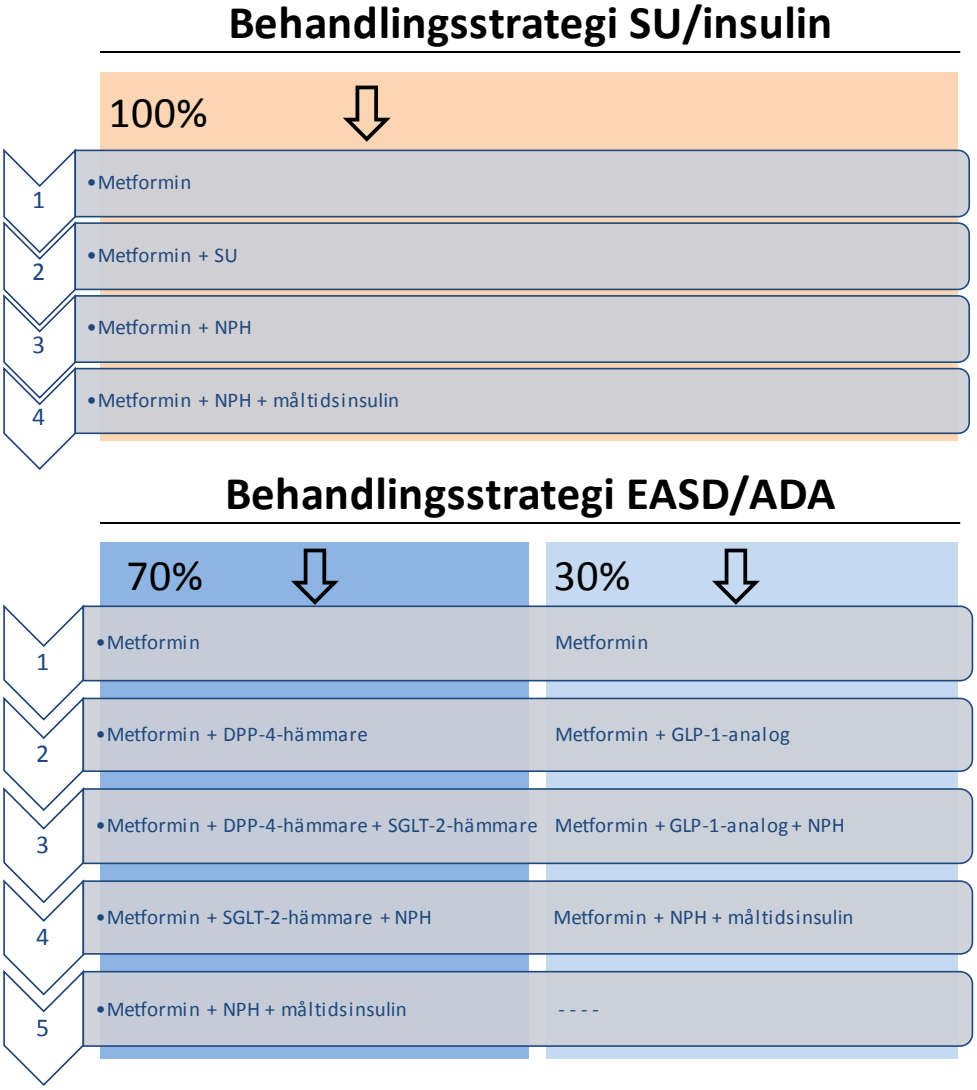
Kohorterna utgjordes av två grupper:

1) Befintliga kohorter år 2013 - prevalent typ 2-diabetes population
2) Nyinsjuknade från år 2013 - framtida incidenta kohorter med typ 2-diabetes

Den prevalenta diabetespopulationen utgjordes av 2 592 kohorter som definierades efter kön, ålder, diabetesduration, rökstatus, nivå på glukoskontroll och nuvarande behandling. Ett exempel på en kohort ur den prevalenta diabetespopulationen är icke-rökande kvinnor i åldersgruppen 40-50 år som levt med diabetes i 2-4 år och behandlas med metformin med en genomsnittlig nivå av måluppfyllnad för HbA1c på 56 mmol/mol. Den incidenta populationen utgjordes av 1 296 kohorter (72 årliga kohorter som insjuknade i typ 2-diabetes) som antogs likna de personer som insjuknar i typ 2-diabetes idag både avseende riskprofiler och antal.

För studien skapades två alternativa behandlingsstrategier för glukossänkande behandling. Den ena behandlingsstrategin omfattade NPH-insulin eller sulfonureider (hädanefter kallad behandlingsstrategi SU/insulin) som första tilläggsbehandling till metformin och är tänkt att likna en situation såsom hittillsvarande vård och i enlighet med svenska riktlinjers förstahandsval för tilläggsläkemedel. Den alternativa behandlingsstrategin baserades på rekommendationer från de europeiska och amerikanska diabetesorganisationerna EASD och ADA. Denna behandlingsstrategi inkluderade DPP-4-hämmare, GLP-1-analoger och SGLT-2-hämmare som tilläggsbehandling till metformin innan insulinbehandling (hädanefter kallad behandlingsstrategi EASD/ADA).

Figur 1 illustrerar ett exempel på en behandlingstrappa för kohorter yngre än 75 år som inte redan står på insulinbehandling. I behandlingsstrategi EASD/ADA får 70% av kohorterna behandling som innehåller DPP-4-hämmare och SGLT-2-hämmare medan 30% får GLP-1-analoger, som tilläggsbehandling till metformin innan insulinbehandling sätts in.



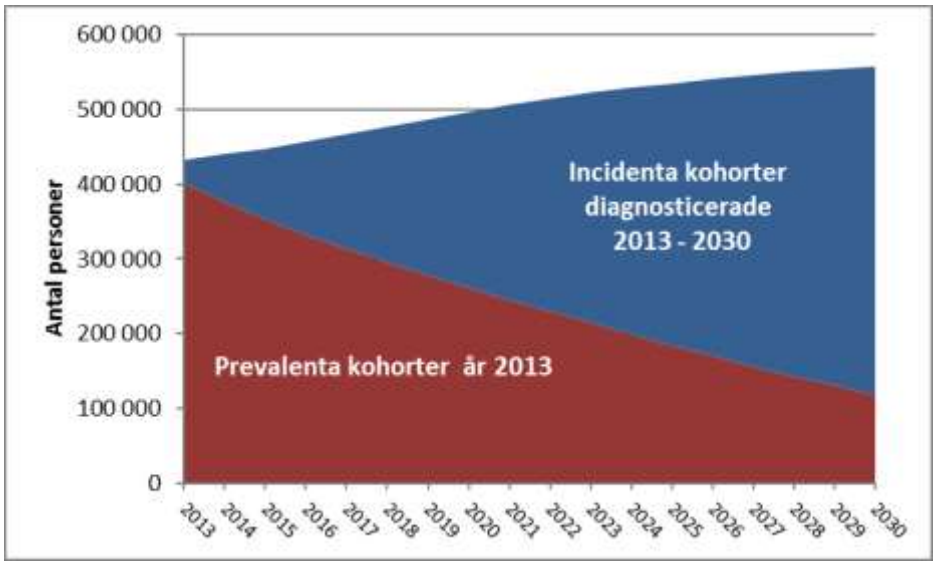
Figur 1 Behandlingstrappa för kohorter yngre än 75 år som inte initialt behandlas med insulin.

Kostnaderna till följd av diabetes analyserades enligt två scenarion. I det första scenariot användes nuvarande prisuppgifter för samtliga ingående läkemedel– hädanefter kallat scenario nuvarande priser. För läkemedlen i behandlingsstrategi EASD/ADA utgår dock patenten i Sverige innan 2030. Exempelvis infaller patentutgång för en GLP-1-analog (Byetta) och en DPP-4-hämmare (Januvia) år 2021, medan patentet för SGLT-2-hämmare (Forxiga) utgår år 2027. I det andra scenariot reducerades därför priserna för läkemedlen i behandlingsstrategi EASD/ADA till följd av framtida patentutgångar – hädanefter kallat scenario patentutgång. I en studie av Intercontinental Marketing Services (IMS) från 2015

skattades prisreduktionen i Sverige till följd av konkurrens från generiska läkemedel till 69% för läkemedel efter patentutgång inom sju olika behandlingsområden[1]. I scenariot med patentutgång reducerades därför kostnadsökningen för glukossänkande behandling för behandlingsstrategi EASD/ADA med 69% för kostnadsanalysen år 2030. Inget av scenarierna tar dock hänsyn till andra framtida händelser som eventuellt kan påverka framtida behandlingskostnader, såsom införandet av nya läkemedel.

Resultat

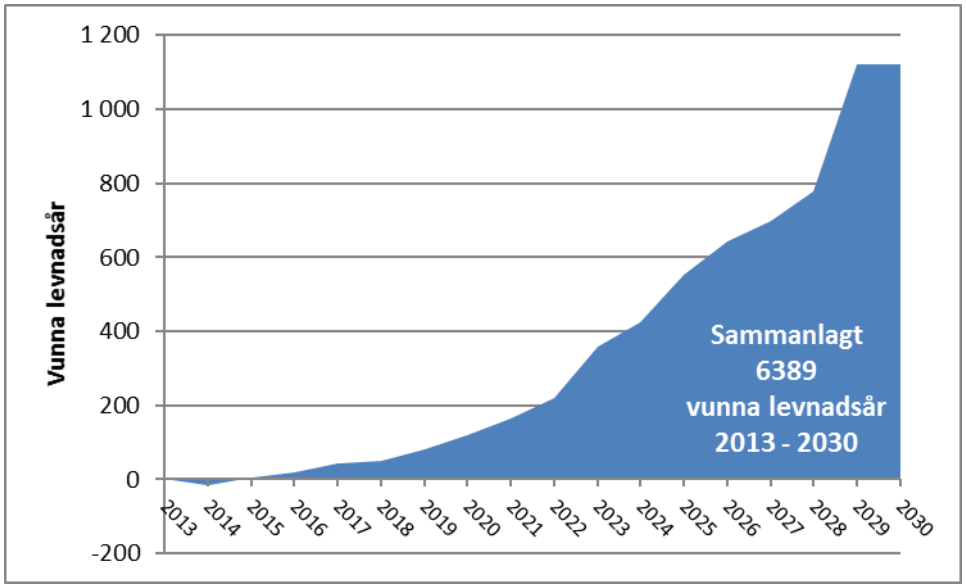
Figur 2 illustrerar antalet personer som förväntas leva med typ 2-diabetes under den analyserade tidsperioden 2013 till 2030. Figuren visar att andelen prevalenta kohorter minskar över tid på grund av mortalitet och behandling av de incidenta kohorterna blir alltmer betydelsefull för behandlingsresultatet av den totala diabetespopulationen.



Figur 2 Antal personer med typ 2-diabetes från de prevalenta kohorterna år 2013 och från de incidenta kohorterna som årligen insjuknar i typ 2 diabetes under åren 2013-2030 i modellens simuleringar enligt behandlingsstrategi SU/insulin.

[1] De sju behandlingsområdena var angiotensin II-antagonister, antidepressiva läkemedel, antiepileptika, neuroleptika, magsårsmedel, kolesterol regulatorer och orala diabetesläkemedel som valdes ut baserat på utbredd användning, konsekvent behandlingsmönster och blandning av generika och varumärken över de europeiska marknaderna.

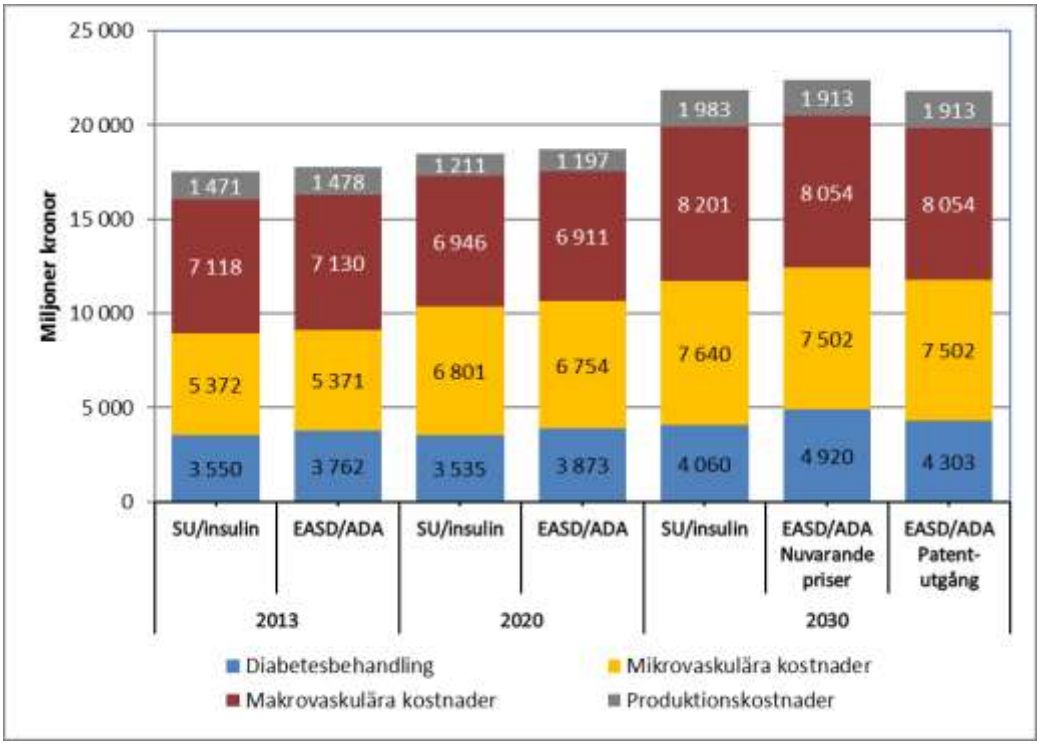
Modellanalysen indikerade att behandlingsstrategi EASD/ADA skulle kunna minska den kumulativa incidensen för mikrovaskulära komplikationer med över 3 000 fall under perioden fram till 2020 och med 10 500 fall under perioden fram till 2030 jämfört med behandlingsstrategi SU/insulin. Motsvarande skattning för makrovaskulära komplikationer var 1 000 färre fall under perioden fram till 2020 och nästan 9 000 färre fall under perioden fram till 2030. Modellanalysen visade även att behandlingsstrategi EASD/ADA leder till en längre överlevnad jämfört med behandlingsstrategi SU/insulin. Figur 3 illustrerar skillnaden i överlevnad mellan behandlingsstrategi EASD/ADA och behandlingsstrategi SU/insulin som summerar till 6 389 vunna levnadsår med behandlingsstrategi EASD/ADA över tidsperioden 2013 till 2030.



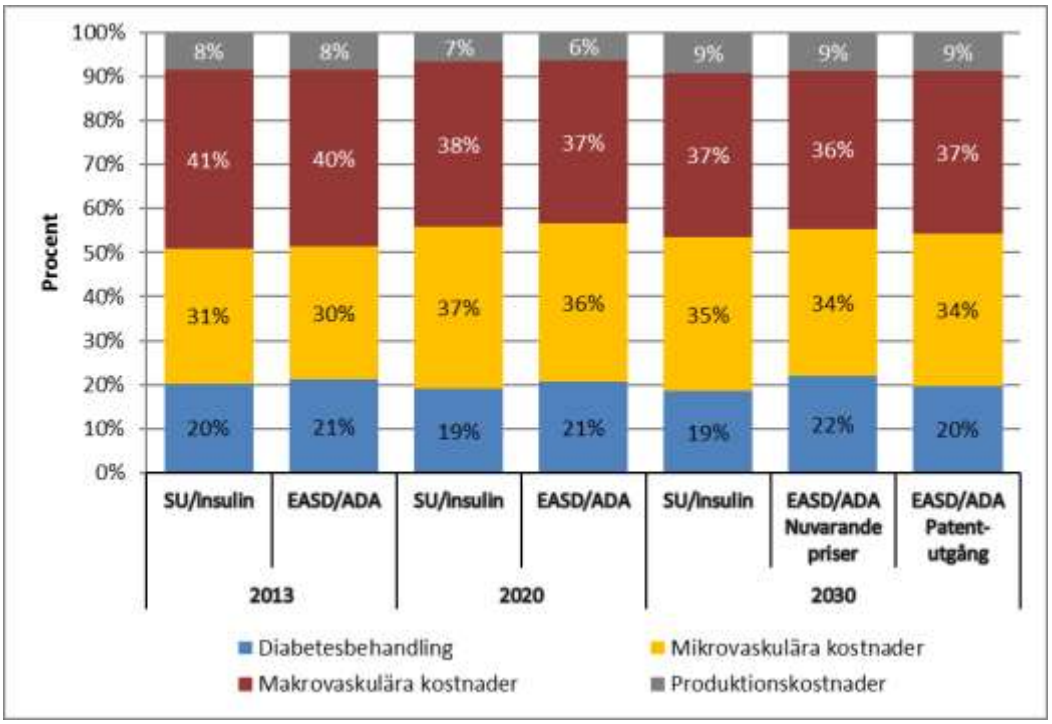
Figur 3 Skillnad antal vunna levnadsår per år och kumulativt för hela perioden 2013-2030 mellan behandlingsstrategi EASD/ADA och behandlingsstrategi SU/insulin.

Den totala kostnaden för typ 2-diabetes enligt behandlingsstrategi SU/insulin skattades till 17,5 miljarder kronor år 2013, 18,5 miljarder kronor år 2020 och 21,9 miljarder kronor år 2030. Enligt scenariot med nuvarande priser förväntas behandlingsstrategi EASD/ADA leda till en ökning av den totala nettokostnaden för typ 2-diabetes med 240 miljoner kronor år 2020 och 500 miljoner kronor år 2030 jämfört med behandlingsstrategi SU/insulin. Enligt scenario patentutgång, som tog hänsyn till prissänkningar till följd av patentutgångar, förväntades behandlingsstrategi EASD/ADA istället leda till en minskning av den totala nettokostnaden för typ 2-diabetes med 113 miljoner kronor år 2030.

Kostnadernas fördelning mellan förebyggande behandling, mikrovaskulära respektive makrovaskulära diabeteskomplikationer samt produktionsförluster för åren 2013, 2020 och 2030 visas i Figur 4 och Figur 5. Kostnadsökningen för behandlingsstrategi EASD/ADA enligt scenariot med nuvarande priser beror på högre kostnader för glukossänkande behandling (nästan 350 miljoner kronor år 2020 och 900 miljoner kronor år 2030). Enligt scenariot med patentutgång var motsvarande kostnadsökning för behandlingsstrategi EASD/ADA knappt 250 miljoner kronor år 2030. Samtidigt förväntas kostnaderna för diabeteskomplikationer vara 82 miljoner kronor lägre år 2020 och 285 miljoner kronor lägre 2030. Kostnadsökningen för glukossänkande behandling sänks med 23 procent år 2020 och med 32 procent år 2030 genom sänkta kostnader för diabeteskomplikationer enligt scenariot med nuvarande priser. Vid scenariot med patentutgång sjunker totalkostnaderna 2030 genom att minskade kostnader för diabeteskomplikationer kompenserar kostnadsökningen för glukossänkande behandling. Utöver detta förväntas behandlingsstrategi EASD/ADA medföra en produktionsökning motsvarande 14 miljoner kronor år 2020 och 71 miljoner kronor år 2030.



Figur 4 Parvis jämförelse av kostnader för behandlingsstrategierna SU/insulin och EASD/ADA. Svenska kronor, fasta priser. Scenario nuvarande priser och scenario patentutgång.



Figur 5 Jämförelse av fördelning av fyra kostnadstyper mellan behandlingsstrategierna SU/insulin och EASD/ADA, procent. Scenario nuvarande priser och scenario patentutgång.

Slutsats

Den modellbaserade analysen skattade färre diabeteskomplikationer till följd av behandlingsstrategi EASD/ADA jämfört med behandlingsstrategi SU/insulin. Skattningen av totalkostnaden år 2030 beror på hur kostnadsberäkningen görs. Vid modellanalysen med läkemedelspriser på 2016 års nivå, leder behandlingsstrategi EASD/ADA till högre totalkostnader år 2030. När hänsyn tas till patentutgångar leder behandlingsstrategi EASD/ADA till minskade totalkostnader år 2030. En aktuell frågeställning är därför om det behövs utökade resurser i diabetesvården för att möjliggöra implementering av behandlingsstrategi EASD/ADA. En utmaning är att resurstillskott framförallt skulle behövas tidigare i primärvården för att kunna erbjuda fler patienter innovativa läkemedel medan kostnadsbesparingarna uppstår först senare i specialistsjukvård och akutsjukvård.

Nyligen publicerade studier visar en ytterligare minskad risk för kardiovaskulär död och vissa kardiovaskulära händelser för typ 2-diabetespatienter med hög kardiovaskulär risk som behandlas med innovativa diabetesläkemedel. Studierna identifierade betydande riskskillnader efter tre års uppföljningstid. Dessa hälsofördelar kommer att fångas enbart av nuvarande modellanalys om de är kopplade till motsvarande effekter på de riskfaktorer som ingår i modellen, såsom inverkan på blodfetter, blodtryck och BMI. Om den minskade risken för hjärtkärlhändelser drivs av andra mekanismer så kan det innebära att modellanalyserna underskattar minskningen av diabeteskomplikationer och överskattar totalkostnaden för behandlingsstrategi EASD/ADA.

1. Background

Type 2 diabetes is a serious disease with potentially fatal consequences. Modern preventive treatment for type 2 diabetes includes lifestyle modification and control of known risk factors such as blood glucose, blood lipids and blood pressure. There is strong scientific evidence that effective risk control reduces the risk of diabetes complications.

The Swedish Institute for Health Economics (IHE) has previously estimated medical costs and costs of production losses due to type 2 diabetes in 2020 and 2030 in Sweden (IHE Report 2015:1). Comparisons were made between current diabetes care designed to resemble the care offered in Sweden today and a more intensive approach with more frequent health care contacts together with additional glucose-lowering treatment and a lower threshold for treatment change (in line with the national guidelines for diabetes care from the National Board of Health and Welfare, NBHW). The analysis showed that a more intensive treatment strategy, in line with the national guidelines, reduces the risk of early death and lead to fewer cases of diabetes complications, while being cost-neutral in 2030.

During the past decade, several drugs with innovative modes of action have been introduced for the treatment of type 2 diabetes. Among those are DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors. Clinical studies have shown that these drug classes have improved risk control through reduced HbA1c, lower blood pressure and BMI and less hypoglycemia. The Swedish national guidelines recommend NPH-insulin as first choice of add-on when metformin alone fails to achieve sufficient glucose control. European and US guidelines from the diabetes associations EASD/ADA recommend individualized glycemic targets and choice of type of glucose-lowering therapies and open up for the use of DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors in second line after metformin [1]. While increased use of these glucose lowering therapies may increase costs of preventive treatment, their properties, in terms of improved risk factor control, may be expected to offset at least part of the cost increase as diabetic complications will be postponed or even avoided.

The aim of this model-based study is to estimate the long-term complications and societal costs of type 2 diabetes in 2020 and 2030 as a result of continuing the current standard of care as provided in Sweden in recent years or a treatment strategy including DPP-4 inhibitors, GLP-1 agonists or SGLT-2 inhibitors as add-on to metformin in second-line treatment.

2. Method

2.1. The IHE Cohort Model of Type 2 Diabetes

The IHE Cohort Model of Type 2 Diabetes [2] was used to estimate costs for cohorts with type 2 diabetes. The cohorts were assigned demographic and clinical characteristics according to statistics from the Swedish National Diabetes Register (NDR) [3] and published studies [4-11]. In the model, the disease is represented by health states that reflect important micro- and macrovascular diabetes complications and death. Microvascular complications include several stages of diabetic retinopathy, kidney disease, neuropathy and peripheral vascular disease. Macrovascular complications consist of myocardial infarction, stroke, ischemic heart disease and congestive heart failure.

Progression of diabetes complications evolves through two parallel Markov chains containing the microvascular and macrovascular complications. For this study, risk equations for macrovascular diabetic complications based on data from the Swedish NDR was used [11]. Risk equations for microvascular diabetic complications were sourced from published studies [12-14] The risks of developing microvascular and macrovascular complications are related to blood glucose level, demographic factors (e.g. age or gender) as well as other risk factors (e.g. smoking or blood pressure level). There is an interaction between complications, where certain complications increase the risk of other complications (e.g. the risk of having a stroke is higher after developing congestive heart failure). For myocardial infarction and stroke the model also include risks for subsequent events after the first myocardial infarction or stroke.

The model also calculates survival based on a set of mortality risk equations. For this study, mortality risk equations based on updated data from the UKPDS study were used [15]. The mortality risk is related to the presence of complications, as well as demographic factors as well as other risk factors. The mortality is highest during the first year in which either an ischemic heart disease, myocardial infarction, congestive heart failure, stroke, amputation, or end stage renal disease first occurs, but the risk is also increased during subsequent years after these events.

The IHE Cohort Model of Type 2 Diabetes can predict costs and quality of life for a cohort up to a time horizon of 40 years. At simulation start the cohort is defined by a large number of demographic and clinical factors, such as age, gender, duration of diabetes, smoking, presence of known cardiovascular disease, and important biomarkers for diabetes such as blood glucose (HbA1c), blood pressure, blood cholesterol, body mass index (BMI).

The model compares two treatment strategies that are defined by the user in terms of effect on biomarkers such as HbA1c, blood pressure, blood lipids and BMI (see Section 2.5 and Table A 8 to Table A 11 in the Appendix).

2.2. Empirical strategy

Costs of diabetes treatment and of diabetes complications depend on the risk profile of the cohort. It is therefore important that the model includes the variation in risk profiles among type 2 diabetes patients in Sweden today. In this study, we divided the population into two groups:

- Prevalent population: The current type 2 diabetes cohorts in 2013
- Incident population: The future newly diagnosed type 2 diabetes cohorts from 2013

Altogether, 421 000 people were estimated to have type 2 diabetes in 2013 based on the National Pharmaceutical Register from the National Board of Health and Welfare and on the number of people with non-pharmaceutical diabetes treatment only registered in the NDR. These people constituted the prevalent type 2 diabetes population, and were divided into a total of 2 592 cohorts defined by diabetes duration, current treatment, level of glucose control, age, gender and smoking status. For example, one cohort from the prevalent diabetes population consisted of non-smoking women, aged 40-50 years, with a diabetes duration of 2-4 years who were treated with metformin with an average level of glucose control of HbA1c of 56 mmol/mol. The design of the cohorts of the prevalent population in 2013 was based on data from the NDR [3] and published studies [4-11]. Details on how the total number of people with type 2 diabetes in 2013 were distributed across the cohorts is described in the Appendix *Profiles of the prevalent population*.

For this study, it was assumed that people who develop type 2 diabetes from 2013 will be similar to the people who develop type 2 diabetes today, both in terms of risk profile and number of cases. These people constituted the incident type 2 diabetes population, and were divided into a total of 72 yearly cohorts (1 296 cohorts in total) defined by level of glucose control, age, gender and smoking status. The design of the future incident cohorts was also based on data from the NDR [3] and on published studies [4-11]. The section *Profiles of the incident population* in the Appendix presents the model's baseline data for incident cohorts.

The IHE Cohort Model of Type 2 Diabetes was used to simulate all cohorts. The model was populated with the 2 592 prevalent cohorts representing the current type 2 diabetes cohorts in 2013 as well as with the 1 296 incident cohorts representing the future newly diagnosed type 2 diabetes cohorts from 2013. While the prevalent cohorts were all started at year 2013, the incident cohorts were started each year, 72 new cohorts every year from 2013 until 2030.

2.3. Cumulative incidence

The model estimates the cumulative incidence of micro- and macrovascular diabetic complications in 2020 and 2030. The incidence of complications is calculated as the total number of complications that occur during the study period (2013 to 2020 and 2013 to 2030, respectively). Hence, the number of complications are summarized up to a certain year for prevalent cohorts and for incident cohorts diagnosed in that year.

2.4. Direct and indirect costs

Total costs are calculated for the cohorts included in the model simulations each year. This is based on a cross section method where costs associated with a specific year are summarized (for 2013, 2020 and 2030, respectively).

Costs presented from the model analysis are direct costs (total costs and separated into costs of preventive treatment and for microvascular and macrovascular complications) and indirect costs of productivity losses. Costs of productivity losses were calculated based on the expected absence from work due to diabetes complications for people in working age. All costs used in the model simulations are in the value of 2013, except for drug costs which are from 2016.

2.5. Treatment strategies

Treatment strategies in the model were determined by the current treatment assigned to the cohort (non-pharmacological treatment, oral therapy or insulin, based on the treatment categories used by the NDR[2]) and by the average age of the cohort. The starting point for the model analysis has been that treatment strategies should reflect current recommendations and treatment guidelines. NBHW treatment guidelines recommends individualized treatment and that strategies should be adopted to the patient's profile including expected remaining life years. Intensive strategies are recommended for patients where effective therapies will reduce diabetic complications that may develop in a 10-15 years' perspective. Moreover, the risk-benefit comparison for elderly patients should also consider consequences of increased risk of falls associated with tight blood glucose control. These factors were operationalized in the present analyses using a simplified division so that patients older than 75 years would have higher threshold values for next blood-glucose lowering therapy adding agents and increasing insulin doses, respectively [16]. This implied that the average HbA1c level before initiating treatment intensification where higher for cohorts older than 75 years compared to younger cohorts. The model was used to illustrate

[2] The treatment classifications used in the NDR do not capture that GLP-1 agonists that are used in the treatment of type 2 diabetes are injected and therefore do not suit neither the category oral therapy nor insulin.

how diabetes complications and costs could be influenced by a more innovative approach to glucose lowering treatment, and cohorts were assigned two alternative treatment strategies:

1) Current standard of diabetes care
2) DPP-4 inhibitors, GLP-1 agonists or SGLT-2 inhibitors in second-line therapy

The first treatment strategy (hereafter called strategy SU/insulin) included an escalation with additional glucose-lowering drugs and increased doses, where the type of drug was selected based on current treatment in Sweden and national recommendations and treatment guidelines. Treatment strategy SU/insulin included metformin, sulphonylurea and insulin (NPH-insulin and mealtime insulin). When another diabetes drug was initiated or the dose increased, it was assumed that the level of HbA1c decreased as shown in published studies. The strategy SU/insulin could also be described as if the diabetes care in the future would essentially be similar to the diabetes care that has been given in recent years. The model's treatment algorithms are described in more detail in the Appendix Table A 8 to Table A 11.

The second treatment strategy (hereafter called strategy EASD/ADA) was based on European and American guidelines and included DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors in second line after metformin. The treatment strategy EASD/ADA also included insulin (NPH-insulin and mealtime insulin) in the final steps when patients failed to achieve glucose control in the first steps. But unlike treatment strategy SU/insulin, it included the innovative treatments dipeptidyl peptidase-4 (DPP-4), Glucagon-like peptide-1 (GLP-1) or sodium/glucose cotransporter-2 (SGLT-2) instead of sulphonylurea. More details on the treatment strategy EASD/ADA can be found in the Appendix Table A 8 to Table A 11.

The treatment sequence for cohorts younger than 75 years who are not initially treated with insulin is illustrated in Figure 1. In treatment strategy "EASD/ADA" 70% of the cohorts receive treatment containing DPP-4 inhibitors and SGLT-2 inhibitors while 30% receive treatment with GLP-1 agonists, in addition to metformin before treatment with insulin is started.

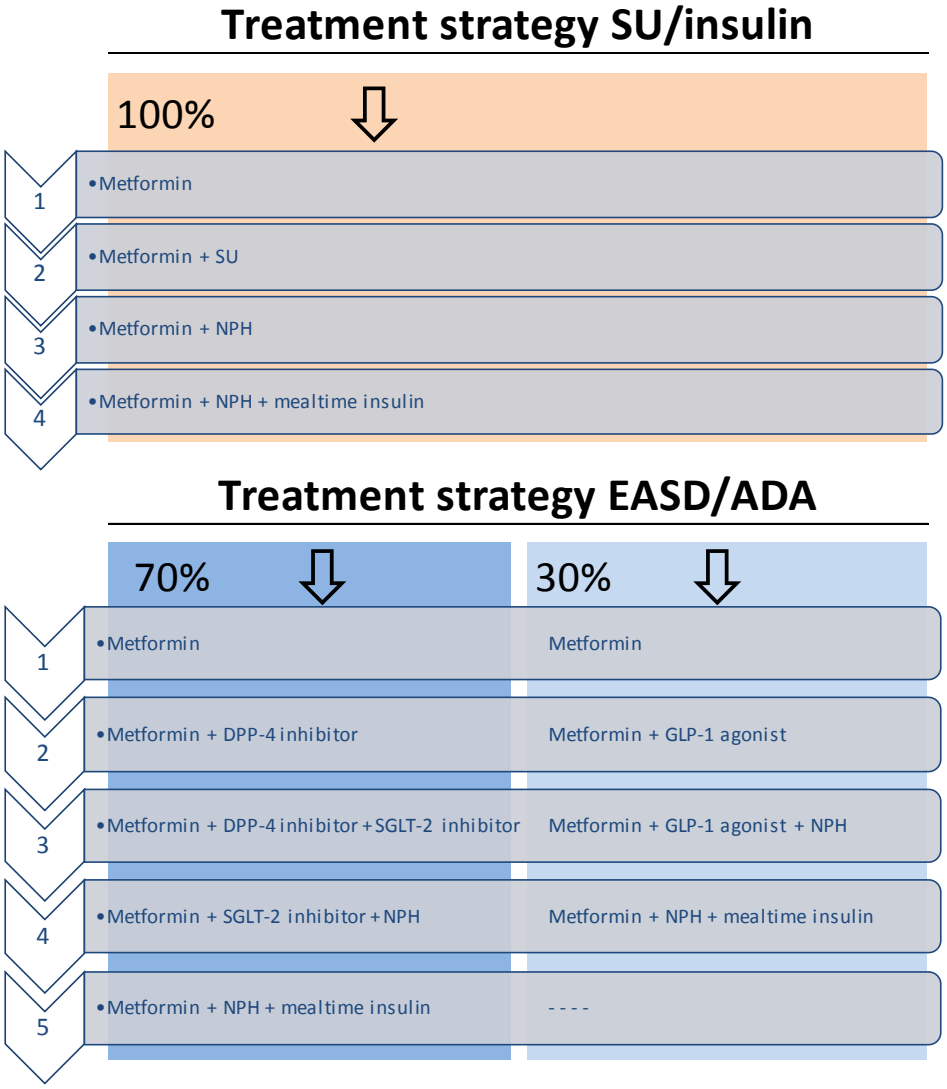


Figure 1 Treatment sequence for cohorts younger than 75 years who are not initially treated with insulin.

For both strategies, the costs were estimated according to three key assumptions in line with the ISPOR recommendations for analysis of budget impact[3]:

- No discounting of costs.
- No development of productivity in health care or the economy at large. This means that the results reflect the costs under the assumption that the efforts made today are also made in the future, for example, in conditions like a myocardial infarction or diabetic retinopathy.
- No development of costs in health care or the economy at large. Prices for interventions in the health care sector and wages for the calculation of costs of production losses are in fixed prices. (Except in scenario patent expiry described below).

With these assumptions, differences in costs will depend on model predictions on how the different treatment strategies determine resource use and risk of diabetes complications. The model estimation of total resource use will be based on the number of people who are living with type 2 diabetes at any time and the health states that they are in. This method enables comparison over time of costs related to different treatment strategies in diabetes care.

The cost of antihyperglycemic treatments for type 2 diabetes was analyzed using two different scenarios. The analysis in the first scenario used the price of 2016 of the branded drugs included in the treatment strategies (hereafter referred to as scenario current prices). However, the drugs included in treatment strategy EASD/ADA will be off-patent in Sweden by year 2030. For example, patent expiry for one GLP-1 agonist (Byetta) and one DPP-4 inhibitor (Januvia) is in year 2021 while patent expiry for one SGLT-2 inhibitor (Forxiga) is in year 2027. In the second scenario (hereafter referred to as scenario patent expiry), prices of the drugs in treatment strategy EASD/ADA were therefor reduced to capture future patent expiry. A recent study from Intercontinental Marketing Services (IMS) estimated a 69% reduction in the price of off-patent drugs in seven chronic disease areas[4] in Sweden following the entrance of generic drugs [17]. In the scenario of patent expiry, the increased cost for antihyperglycemic treatment in treatment strategy EASD/ADA were reduced by 69%. However, none of the scenarios are taking into account other future events that could possibly affect future treatment costs, such as the entry of new innovative drugs.

[3] ISPOR is an international organization for Pharmacoeconomics and outcomes research with the aim of translating research findings into useful information for decision-makers (http://www.ispor.org).
[4] The seven therapeutic areas were angiotensin II antagonists, antidepressants, anti-epileptics, antipsychotics, anti-ulcerants, cholesterol regulators and oral antidiabetics which were selected based on broad usage and consistent treatment pattern and mix of generics and brands across European markets.

3. Material

3.1. Definition of cohorts

For the model estimation, we defined 1 944 cohorts for people in the prevalent population with type 2 diabetes and 1 296 cohorts of people with newly diagnosed diabetes between 2013 and 2030 (72 new incident cohorts each year). The total number of cohorts was designed based on the properties that were used to characterize these cohorts. Data from the NDR was a central source to identify different characteristics of the cohorts and to estimate the number of persons in each cohort. We used the annual report and the online database from the NDR [3] as well as data from relevant publications [4-11]. The prevalent and incident cohorts differed regarding the input profile they were assigned.

The prevalent cohorts were designed based on their diabetes duration, current treatment, achievement of glycemic control (HbA1c), age, gender and smoking status. In addition to age, gender and smoking status, the incident cohorts were defined by risk profile, which indicates whether the cohort has a low/medium/high risk profile.

Using published and aggregated data, the cohorts were designed to reflect characteristics of people with type 2 diabetes in Sweden as far as possible. In some cases, the expected number of people in a cohort was limited. For example, there are few people who develop type 2 diabetes before the age of 30. This means that the number of incident cohorts estimated was less than the number of theoretically possible combinations.[5] The characteristics of the prevalent and incident cohorts are reported in the Appendix section *Profiles of the prevalent population* and *Profiles of the incident population*.

The annual report from the NDR for 2014 with results from 2013 reported 352 388 people with diabetes, where type 2 diabetes accounted for the vast majority including 10 146 people (3%) treated in specialist care and 303 403 people (86%) treated in primary care. Since specialist care represents a small proportion, we used results reported for type 2 diabetes in primary care when data on the total population of type 2 diabetes was not available.

3.2. The number of people with diabetes

To calculate the difference in expected future costs of diabetes, we made assumptions about the number of people with diabetes in the prevalent population in 2013 and the number of people that each year are diagnosed with diabetes up to 2030. The prevalence of type 2 diabetes in Sweden in 2013 was estimated to about 421 000 people based on the number of patients with at least one used prescription of a diabetes drug according to the National

[5] Theoretically there were 8*2*3*2=96 possible combinations of incident cohorts. Some combinations were deemed unlikely, for instance young age combined with long duration of diabetes, and was not included.

Pharmaceutical Register from the NBHW and treatment data on people with diabetes registered in the NDR. This figure formed the basis for the allocation of people into the prevalent cohorts. A more detailed description of the strategies to distribute the prevalent population into the 1 944 cohorts are reported in the Appendix *Profiles of the prevalent population*.

Regional studies aggregated to a national level estimated the number of newly diagnosed patients with type 2 diabetes to be somewhere between 29 000 and 35 000 in 2011 [18]. A study based on the National Pharmaceutical Register from the NBHW and data from the NDR reports an annual incidence of diabetes of between 33 000 and 35 000 people between 2006 and 2013. The study could not separate between different types of diabetes, but patients with type 2 diabetes constitutes the majority of the newly diagnosed population [19]. In this report we have assumed that 33 000 people are diagnosed with type 2 diabetes each year until 2030.[6] Details of the estimation on the number of people in the incident cohorts can be found in the previous study (IHE Report 2015:1) and in the Appendix *Profiles of the incident population*.

3.3. Input data

The following input data were used in the model estimations

- Demographic and clinical characteristics of the cohorts
- Treatment algorithms for the gradual intensification of glucose lowering treatment to achieve targets for blood glucose level
- Threshold values for initiation of antihypertensive and lipid-lowering treatment
- Treatment costs including costs for drugs, physician visits and blood glucose testing
- Direct and indirect costs of hypoglycemic events
- Direct and indirect costs of micro- and macrovascular complications including expenses for an acute event and expenses for a person in the actual state of the complication of diabetes (annual cost)

Details on the input data used in the model estimations can be found in the Appendix.

[6]To assume a constant number of patients diagnosed with diabetes each year is a conservative assumption since population growth implies a gradual increase in the number of people with diabetes.

4. Results

The number of people who are expected to live with type 2 diabetes during 2013 to 2030 are illustrated in Figure 2. The figure shows that the proportion of prevalent cohorts are decreasing over time due to mortality and the treatment of incident cohorts will be become more important in terms of treatment outcomes for the total diabetes population.

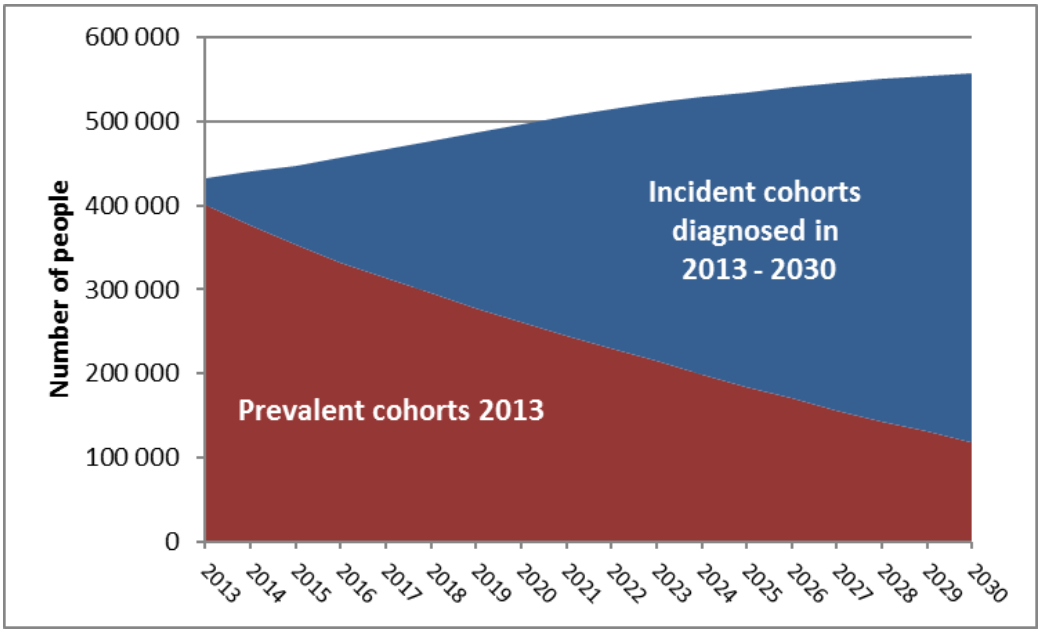


Figure 2 The number of people with type 2 diabetes from the prevalent cohorts in 2013 and from de incident cohorts who each year are diagnosed with type 2 diabetes during 2013-2030 from the model simulations for treatment strategy SU/insulin.

4.1. Cumulative incidence of complications

The difference in cumulative incidence of complications between treatment strategy SU/insulin and treatment strategy EASD/ADA in 2020 is presented in Table 1. The cumulative incidence of complications in 2020 was generally lower for treatment strategy EASD/ADA than for SU/insulin. The largest reduction was seen for background diabetic retinopathy where the cumulative incidence decreased by 930 cases. In total, the cumulative incidence of diabetes complications in 2020 was estimated to decrease by over 3 000 cases due to microvascular complications and by over 1 000 cases due to macrovascular complications for treatment strategy EASD/ADA compared to SU/insulin.

Table 1 The difference in cumulative incidence of complications between treatment strategy EASD/ADA and SU/insulin in years 2013-2020.

	Absolute difference	Relative difference [a)]
Microvascular complications	**-3 011**	**-0.55%**
Retinopathy		
Background diabetic retinopathy	-930	-0.77%
Proliferative diabetic retinopathy	-21	-0.27%
Macular edema	-473	-1.10%
Severe vision loss	-36	-0.53%
Neuropathy		
Symptomatic neuropathy	-265	-0.43%
Peripheral vascular disease	13	0.01%
Nephropathy		
Microalbuminuria	-616	-0.45%
Macroalbuminuria	-647	-1.28%
End stage renal disease	-36	-0.43%
Macrovascular complications	**-1 032**	**-0.27%**
Ischemic Heart Disease	-327	-0.30%
Myocardial Infarction	-334	-0.38%
Stroke	-6	-0.01%
Congestive Heart Failure	-365	-0.32%

[a)] Calculated as the difference in cumulative incidence between treatment strategy EASD/ADA and SU/insulin divided by the total cumulative incidence of treatment strategy SU/insulin

The difference in cumulative incidence of complications between treatment strategy SU/insulin and EASD/ADA in 2030 is presented in Table 2. The cumulative incidence of complications in 2030 was generally lower for treatment strategy EASD/ADA than for SU/insulin and the difference was increased compared to 2020. The largest reduction was seen for congestive heart failure where the cumulative incidence was estimated to decrease by 5 000 cases, followed by cumulative incidence for background diabetic retinopathy which was estimated to decrease by almost 4 000 cases. In total, the cumulative incidence of diabetes complications in 2030 was estimated to decrease by 10 500 cases due to micro-vascular complications and by almost 9 000 cases due to macrovascular complications for treatment strategy EASD/ADA compared to SU/insulin.

Table 2 The difference in cumulative incidence of complications between treatment strategy EASD/ADA and SU/insulin in years 2013-2030.

	Absolute difference	Relative difference [a)]
Microvascular complications	**-10 520**	**-1.24%**
Retinopathy		
Background diabetic retinopathy	-3 946	-2.39%
Proliferative diabetic retinopathy	-243	-2.42%
Macular edema	-1 325	-1.91%
Severe vision loss	-195	-1.19%
Neuropathy		
Symptomatic neuropathy	-764	-1.05%
Peripheral vascular disease	158	-0.08%
Nephropathy		
Microalbuminuria	-1 542	-0.71%
Macroalbuminuria	-2 278	-2.82%
End stage renal disease	-385	-2.27%
Macrovascular complications	**-8 823**	**-1.21%**
Ischemic Heart Disease	-1 364	-0.74%
Myocardial Infarction	-1 514	-0.89%
Stroke	-930	-0.61%
Congestive Heart Failure	-5 015	-2.23%

[a)] Calculated as the difference in cumulative incidence between treatment strategy EASD/ADA and SU/insulin divided by the total cumulative incidence of treatment strategy SU/insulin

The model analysis also indicated that treatment strategy EASD/ADA results in a higher survival rate compared to treatment strategy SU/insulin. Figure 3 illustrates the difference in survival rate between treatment strategy EASD/ADA and SU/insulin, which adds ups to 6 389 life years gained during the period 2013 to 2030.

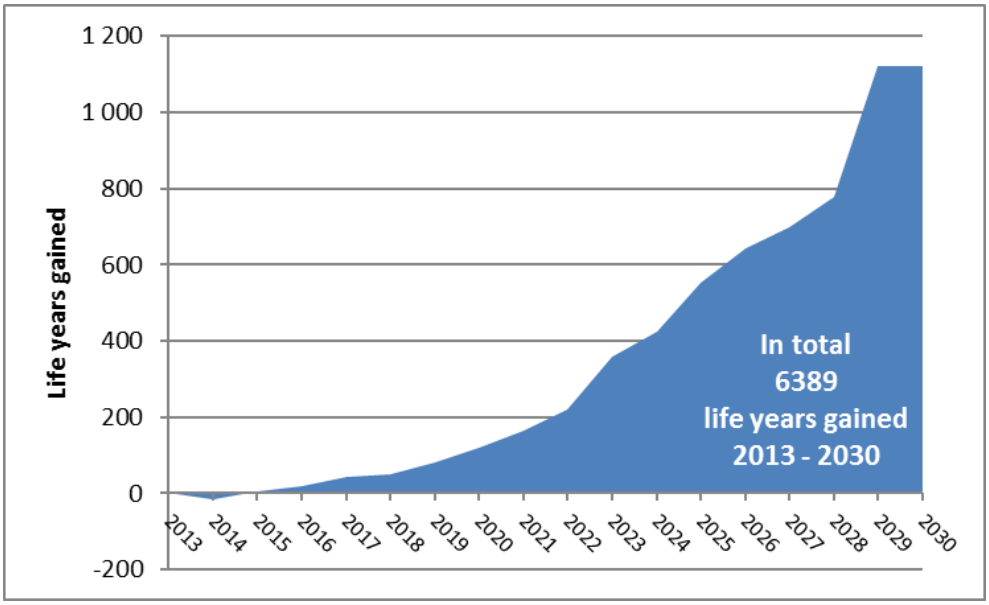


Figure 3 Difference in life years gained yearly and cumulative for the time period 2013-2030 between treatment strategy EASD/ADA and treatment strategy SU/insulin

4.2. Costs per year in 2020 and 2030

The estimated costs of treatment strategy SU/insulin and EASD/ADA in 2020 are presented in Table 3. The total costs of treatment strategy SU/insulin in year 2020 were estimated to SEK 18.5 billion, where SEK 3.5 billion were constituted by costs of diabetes treatment (19%), SEK 6.8 billion by costs of microvascular complications (37%), SEK 6.9 billion by costs of macrovascular complications (38%) and SEK 1.2 billion by indirect costs (7%). The majority of the costs for diabetes treatment were assigned costs of antihyperglycemic treatment (SEK 2.4 billion), followed by costs of treatment of dyslipidemia (SEK 785 million), hypertension (SEK 283 million) and hypoglycemia (SEK 34 million).

Treatment strategy EASD/ADA was estimated to increase the total costs by SEK 242 million in 2020 compared to treatment strategy SU/insulin. Costs of diabetes treatment increased by a total of SEK 338 million, where antihyperglycemic costs increased by SEK 344 million and costs of hypertension and hypoglycemia decreased by SEK 2 million and SEK 3 million respectively. The increase in costs of diabetes treatment was partially offset by decreases in costs of microvascular complications (SEK 47 million), macrovascular complications (SEK 35 million) and by indirect costs (SEK 14 million). The largest cost decrease was seen for nephropathy (SEK 35 million) while the second largest cost decrease was assigned costs of congestive heart failure (SEK 16 million).

Table 3 Costs in 2020 of treatment strategy SU/insulin, treatment strategy EASD/ADA and the difference between the two strategies (SEK million in fixed prices)

	Strategy SU/insulin	Strategy EASD/ADA	Difference
Diabetes treatment	**3 535**	**3 873**	**338**
Antihyperglycemic	2 432	2 776	344
Hypertension	283	281	-2
Dyslipidemia	785	786	0
Hypoglycemia	34	31	-3
Microvascular complications	**6 801**	**6 754**	**-47**
Retinopathy	596	589	-7
Neuropathy	2 581	2 576	-4
Nephropathy	3 624	3 589	-35
Macrovascular complications	**6 946**	**6 911**	**-35**
Ischemic Heart Disease	744	738	-6
Myocardial Infarction	646	641	-6
Stroke	4 787	4 780	-7
Congestive Heart Failure	769	753	-16
Indirect	**1 211**	**1 197**	**-14**
TOTAL	**18 492**	**18 734**	**242**

The analysis of the costs of diabetes in 2030 included two separate scenarios. The first scenario used the current prices for all drugs while the second scenario estimated new prices to capture the effect of future patent expiry. The estimated costs of treatment strategy SU/insulin and EASD/ADA for both scenarios are presented in Table 4. The total costs of treatment strategy SU/insulin were estimated to SEK 21.9 billion in 2030. More than two thirds (72%) of the costs were constituted by costs of macrovascular complications (SEK 8.2 billion) and microvascular complications (SEK 7.6 billion) combined. Costs of stroke alone was estimated to SEK 5.6 billion while nephropathy was estimated to cost SEK 4.5 billion. The costs of diabetes treatment were SEK 4.0 billion of which almost SEK 3.0 million was assigned costs of antihyperglycemic treatment.

Treatment strategy EASD/ADA using current prices was estimated to increase the total costs by SEK 503 million in 2030 compared to treatment strategy SU/insulin. Costs of diabetes treatment was estimated to increase by SEK 860 million while the antihyperglycemic treatment cost alone increased by SEK 894 million. At the same time, costs of macrovascular complications decreased by SEK 147 million, costs of microvascular complications decreased by SEK 138 million and indirect costs decreased by SEK 71 million. The largest cost decrease was seen for nephropathy (SEK 118 million), followed by costs of congestive heart failure (SEK 61 million) and stroke (SEK 52 million). Cost of hypoglycemia was estimated to decrease with SEK 35 million.

Table 4 Costs in 2030 of treatment strategy SU/insulin and treatment strategy EASD/ADA for scenario fixed prices and scenario patent expiry (SEK million in fixed prices)

	Strategy SU/insulin	Strategy EASD/ADA		Difference vs SU/insulin	
		Current prices	Patent expiry	Current prices	Patent expiry
Diabetes treatment	**4 060**	**4 920**	**4 303**	**860**	**243**
Antihyperglycemic	2 998	3 892	3 275	894	277
Hypertension	270	268	268	-2	-2
Dyslipidemia	736	738	738	3	3
Hypoglycemia	56	21	21	-35	-35
Microvascular complications	**7 640**	**7 502**	**7 502**	**-138**	**-138**
Retinopathy	488	471	471	-17	-17
Neuropathy	2 610	2 606	2 606	-4	-4
Nephropathy	4 542	4 424	4 424	-118	-118
Macrovascular complications	**8 201**	**8 054**	**8 054**	**-147**	**-147**
Ischemic Heart Disease	838	820	820	-17	-17
Myocardial Infarction	801	784	784	-18	-18
Stroke	5 575	5 524	5 524	-52	-52
Congestive Heart Failure	988	927	927	-61	-61
Indirect	**1 983**	**1 913**	**1 913**	**-71**	**-71**
TOTAL	**21 886**	**22 389**	**19 704**	**503**	**-113**

Treatment strategy EASD/ADA in the scenario of patent expiry was estimated to decrease the total costs by SEK 113 million in year 2030 compared to treatment strategy SU/insulin. The cost of antihyperglycemic treatment for treatment strategy EASD/ADA was SEK 617 million lower in the scenario of patent expiry compared to the scenario of current prices. The difference in estimated costs between treatment strategy SU/insulin and EASD/ADA using the two scenarios of drug prices is illustrated in Figure 4 and Figure 5.

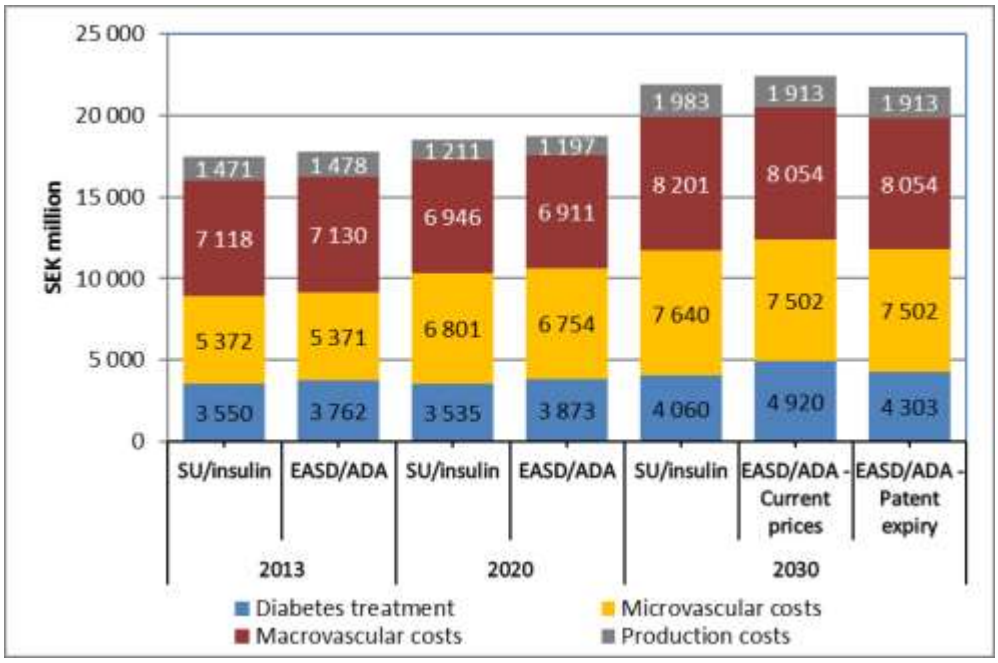


Figure 4 Comparison of costs between treatment strategy SU/insulin and EASD/ADA for scenario current prices and patent expiry (SEK million in fixed prices).

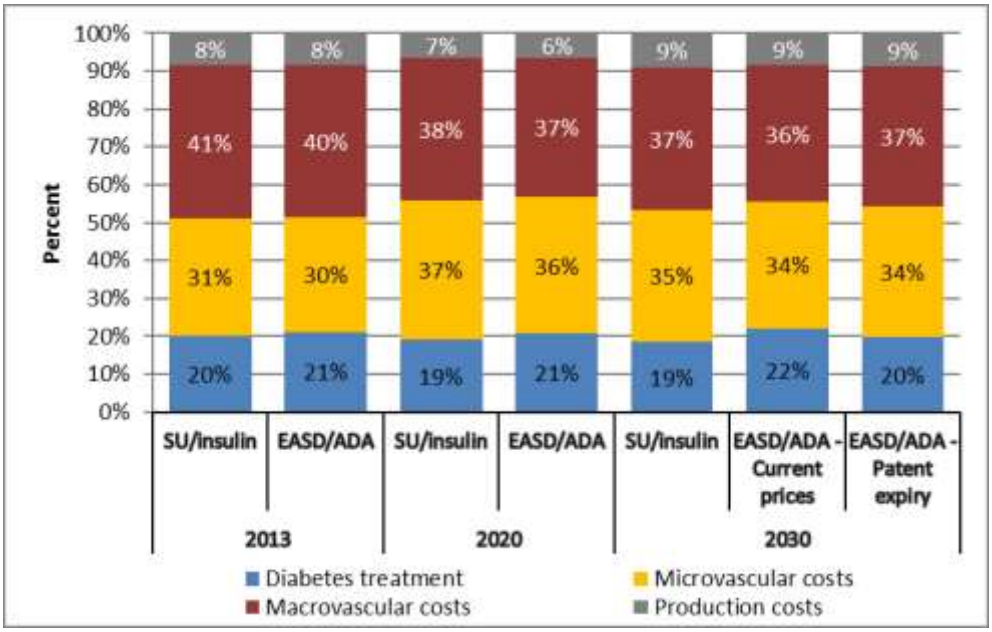


Figure 5 Comparison of costs between treatment strategy SU/insulin and EASD/ADA for scenario current prices and patent expiry (percentage).

5. Discussion

In this report we estimated the long-term complications and societal costs of type 2 diabetes in 2020 and 2030 as a result of a treatment strategy including DPP-4 inhibitors, GLP-1 agonists or SGLT-2 inhibitors as add-on to metformin in second-line treatment compared to current care as provided in Sweden in recent years.

The results from the model-based analysis indicated that the cumulative incidence of diabetes complications would decrease by over 3 000 cases by 2020 and 10 500 cases by 2030 due to microvascular complications for treatment strategy EASD/ADA compared to treatment strategy SU/insulin. Corresponding reductions for macrovascular complications were more than 1 000 fewer cases by 2020 and almost 9 000 fewer cases by 2030. Further, the treatment strategy EASD/ADA was estimated to result in a higher survival rate, which added up to 6 389 life years gained during the time period 2013 to 2030.

In the scenario of current prices, the total costs were estimated to increase by SEK 240 million in 2020 and by SEK 500 million in 2030 for treatment strategy EASD/ADA compared to treatment strategy SU/insulin. The increase in costs of strategy EASD/ADA was attributed to a higher cost for antihyperglycemic treatment (almost SEK 350 million in 2020 and SEK 900 million in 2030), which was partly offset by decreases in costs of microvascular and macrovascular complications and by indirect costs (almost SEK 100 million in 2020 and 350 million in 2030). The lower costs of microvascular and macrovascular complications associated with treatment strategy EASD/ADA can be explained by the estimated decrease in diabetes complications.

By study design, in the scenario with current prices, the difference in predicted future costs are conservative as potential price changes in drugs due to patent expiry and competition is not included. In addition to the drug costs, the antihyperglycemic treatments include costs of blood glucose measurement and for medical visits (Table A 12 in the Appendix). The costs of visits were the same for all treatment alternatives while the costs of blood glucose measurement were higher for insulin than for oral treatments. Therefore, the non-drug costs were the same for DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors as for metformin or sulphonylurea. As a result, while the absolute cost for antihyperglycemic treatments in both treatment strategies included non-drug costs, most of the difference in the costs of antihyperglycemic treatments was due to the costs of the innovative drugs per se.

In the scenario of patent expiry, which explored potential cost savings for payers from future patent expiry of DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors, we found that treatment strategy EASD/ADA could even decrease the total costs by SEK 113 million in year 2030 considering a reduction in the costs of antihyperglycemic treatment. The cost for antihyperglycemic treatment for treatment strategy EASD/ADA was SEK 617 million lower

when future patent expiry was considered compared to current prices. These estimations where based on a historic 69% price reduction seen in off-patent drugs in Sweden. It is, however, possible that the price reductions due to patent expiry in 2030 could be both smaller or larger as the result of a degree of competition in the generic market.

In a previous report, IHE have demonstrated that a more intensive treatment strategy, in line with national guidelines, could reduce the disease burden in the form of diabetes-related mortality and diabetes complications, while being cost-neutral in 2030. While the previous report focused on the effect of a lower threshold for treatment change, the current report used the same thresholds for treatment change in both strategies. The focus of the current report is instead the addition of the newer drugs DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors to the treatment algorithm. Another difference between the two reports is that the current report includes SU as a part of the current standard of diabetes care while the previous report did not. The complications and costs estimated by the model analysis cannot be directly compared since the complications are presented as the cumulative incidence and hence summarized over the whole time period up to a specific year. Costs on the other hand, are calculated and presented for one specific year. To fully analyze the value of the decrease in diabetes complications in relation to the higher cost attributed to the innovative treatment strategy, a cost-effectiveness analysis is required in addition to the budget impact analysis conducted in this study.

A model simulation is a simplification of reality, and as such requires certain assumptions regarding the cohort and treatments. A limitation of this study was the lack of Swedish data for some of the model input. For instance, no Swedish update of risk equations for microvascular complications were available at the time for this study, and instead we used equations from international published studies. On the other hand, risk equations for macro-vascular diabetic complications based on relatively recent data from the Swedish National Diabetes Register (NDR) was used in the model-analysis. Furthermore, the cohorts were assigned demographic and clinical characteristics according to statistics from the NDR and great efforts were undertaken to ensure that study cohorts would resemble the current Swedish population of patients with typ-2 diabetes.

Additionally, recently published results based on observational and randomized controlled trial data provide evidence for reduced risk of cardiovascular death and some cardiovascular events for people with type 2 diabetes and high cardiovascular risk treated with the newer glucose-lowering drugs [20-23]. The randomized controlled trials identified significant risk differences after three-year follow up. These health benefits will be captured in the current analysis to the extent that they are linked to a favorable impact on risk factors measured in the model such as blood lipids, blood pressure and BMI impact. If other and unmeasured mechanisms are driving the effect on risk for cardiovascular death or disease, our estimates

will underestimate the benefits of treatment with DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors. We used the NDR equations for risk of macrovascular complications. These risk equations are based on data from 2003-2008, a period before the introduction of innovative drugs in Swedish type 2 diabetes care. It would therefore be valuable, from a health economic point of view, to revisit the absolute risk equations for diabetic complications using up to date NDR data that provides evidence on real world outcomes of current Swedish diabetes care.

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Appendix

Profiles of the prevalent population

The model input values for the prevalent population with type 2 diabetes in 2013 were based on data from the NDR [3] and from published studies [4-11]. We started from the published results that were reported at the group level and made assumptions for each cohort. Ekström and co-authors analyzed 163 121 people with type 2 diabetes who were registered in the NDR in 2009 [4]. The report describes risk factors for 13 subsamples defined by type of blood-glucose-lowering treatment. These treatments can be categorized as treatment with diet, oral therapy or oral therapy and insulin. The average duration of diabetes is reported for each treatment category and using the standard deviation we could calculate a maximum and minimum duration that was used to estimate the number of people in each treatment group within different duration intervals. These duration intervals are based on classifications in the NDR and are 0-4 years, 5-9 years, 10-14 years, 15-19 years, 20-24 years and 25 years and older.

This study combined information from two sources based on data from NDR to design the prevalent cohorts both by type of treatment and by duration interval [4, 7]. Ekström and co-authors reported information on patients who used different types of glucose-lowering drugs, but limited data on treatment duration. The annual report from the NDR contained information on the distribution of duration intervals but less information about the type of glucose lowering treatment [7]. Data on patients having a diabetes duration more than 25 years was sourced from the NDR [3]. The distribution of the cohorts was made based on the 163 121 people with type-2 diabetes who were included in the study from the NDR [4] adjusted by the ratio between the total prevalence in 2013 calculated from the National Pharmaceutical Register from the NBHW [24] (420 960 people with type 2 diabetes).

It was further assumed that the cohorts belonged to one of three current HbA1c levels; <52 mmol/mol, 52 to 73 mmol/mol or >73 mmol/mol, and to one of nine different age intervals. The age intervals were based on categories used in the NDR: 18-39 years, 40-50 years, 51-55 years, 56-60 years, 61-65 years, 66-70 years, 71-75 years, 76-80 years, and 81 years or older. The median in each age interval was used in the model estimations. The compilation of the number of people in each category of treatment combined with levels of target for HbA1c and age intervals was based on data from the NDR [3].

Since the model separates the cohorts by gender and smoking status, four different categories of cohorts were analyzed for each treatment- and age group; non-smoking men, smoking men, non-smoking women and smoking women. The number of younger cohorts (younger than 75 years) within each treatment category was 504 and the number of older cohorts (75

years and older) within each treatment category was 144, leading to 2592 cohorts in total. Costs of each individual cohort were weighted depending on the size of the cohort in order to obtain the total cost. Small cohorts, such as young people with long duration of diabetes, had less impact on the overall costs because few people belonged to these groups.

Risk factors for prevalent cohorts

Starting values and sources for risk factors for men and women in different age intervals are presented in Table A 1 below. Three levels of HbA1c-value at baseline were applied to all age intervals: 50, 56 and 80 mmol/mol. Values of triglycerides, heart rate, white blood cells and glomerular filtration rate were not reported by gender and age, so they are therefore assumed to be the same for all cohorts.

Table A 1 Risk factors in different age intervals in the prevalent diabetes population, model input data

	Age interval (year)									
Risk factor	**18-39**	**40-50**	**51-55**	**56-60**	**61-65**	**66-70**	**71-75**	**76-80**	**81+**	**Source**
Men										
Systolic blood pressure (mm Hg)	127.7	131.1	132.8	134.3	135.2	135.5	135.3	135.3	134.9	[25]
Diastolic blood pressure (mm Hg)	79.9	81.8	81	79.9	78.4	76.7	75	73.5	72	[25]
Total cholesterol (mmol/l)	4.8	5.1	4.8	5.1	4.8	5.1	5.1	4.8	4.8	[24][a)]
LDL cholesterol (mmol/l)	2.85	2.81	2.72	2.65	2.58	2.49	2.46	2.44	2.43	[25]
HDL cholesterol (mmol/l)	1.2	1.15	1.20	1.15	1.20	1.15	1.15	1.20	1.20	[24][a)]
Triglycerides (mmol/l)	2.19	2.19	2.19	2.19	2.19	2.19	2.19	2.19	2.19	[26]
BMI (kg/m^2)	32.6	31.7	31	30.4	30	29.6	29	28.4	27.1	[25]
Heart rate (bpm)	72	72	72	72	72	72	72	72	72	[26]
White blood cells (1x10^6)	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	[26]
Glomerular filtration rate (ml/min/1.73m^2)	77.5	77.5	77.5	77.5	77.5	77.5	77.5	77.5	77.5	[26]
Women										
Systolic blood pressure (mm Hg)	121.1	127.3	130.4	132.5	134.2	135.6	136.5	137.5	138.6	[25]
Diastolic blood pressure (mm Hg)	76.7	78.8	79	78.2	77.1	75.9	74.5	73.5	72.7	[25]
Total cholesterol (mmol/l)	5.2	4.7	5.2	4.7	5.2	4.7	4.7	5.2	5.2	[24][a)]
LDL cholesterol (mmol/l)	2.86	2.89	2.89	2.85	2.77	2.70	2.65	2.64	2.75	[25]
HDL cholesterol (mmol/l)	1.5	1.2	1.5	1.2	1.5	1.2	1.2	1.5	1.5	[24][a)]
Triglycerides (mmol/l)	2.19	2.19	2.19	2.19	2.19	2.19	2.19	2.19	2.19	[26]
BMI (kg/m^2)	33.2	32.6	32.2	31.5	31.1	30.5	30	29.3	27.8	[25]
Heart rate (bpm)	72	72	72	72	72	72	72	72	72	[26]
White blood cells (1x10^6)	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	[26]
Glomerular filtration rate (ml/min/1.73m^2)	77.5	77.5	77.5	77.5	77.5	77.5	77.5	77.5	77.5	[26]

[a)] Selection of data included in Kiadaliri et al (2013) and compiled as a basis for the international validation meeting for diabetes models: Mount Hood Challenge 2012.

Risk equations for macrovascular and microvascular complications were used for the model analysis [11-14, 27], where the user specifies the proportion of the cohort with at least one previous macrovascular or microvascular event. For example, the incidence of a previous

myocardial infarction affects the risk of the occurrence of another myocardial infarction. The proportion of macrovascular complications that occurred before the diagnosis of diabetes was assumed to apply only to the older age group, and was based on estimates from the NDR. According to these data, 6% had been afflicted by ischemic heart disease, 3% by myocardial infarction, 5% by stroke, and 3% by heart failure before the diagnosis of diabetes [11].

Microvascular risk factors

A study from 2010 analyzed the prevalence and costs of diabetic retinopathy based on a population of 12 026 diabetic patients in Östergötland in Sweden [5]. The prevalence of the different types of diabetes retinopathy were presented by gender, and the data used in the model are reported in Table A 2. No baseline prevalence of blindness was assumed based on a Swedish study [28].

Table A 2 Prevalence of different types of diabetes retinopathy at baseline

Complication	Men	Women	Source
Background Retinopathy (%)	23.5	21.5	[29]
Proliferative retinopathy (%)	1.6	1.0	[29]
Macular edema [a)] (%)	2.7	2.5	[29]
Proliferative retinopathy & Macular edema (%)	1.3	0.9	[29]
Blindness (%)	0	0	[28]

[a)] Assumed same as Maculopathy in Heintz et al (2010)

The prevalence of neuropathy was based on population data from Sundbyberg in Sweden including 156 patients with type 2 diabetes [6]. The prevalence of peripheral vascular disease was reported for the total sample with 26%. The prevalence of symptomatic neuropathy, which was assumed to be the same as polyneuropathy, was reported separately for men and women (27% for men and 22% for women). These values were only used in the model for cohorts older than 60 with at least five years' duration of diabetes. For remaining cohorts, the prevalence of neuropathy at baseline was assumed to be zero.

The model separates between three types of nephropathy; microalbuminuria, macro-albuminuria and end stage renal disease. In the annual report of 2014 from the NDR the prevalence of micro- and macroalbuminuria for patients with different duration of diabetes is reported for primary care [7]. These values were used in the model and assumed to apply to all cohorts depending on duration of diabetes. The baseline prevalence of end stage renal disease was based on Maria Svensson's presentation "Diabetes och njurar" from the department of nephrology at Sahlgrenska University Hospital [10], and assumed to apply only in patients with over ten years of diabetes duration. The baseline values used for nephropathy are reported in Table A 3.

Table A 3 Prevalence of different types of nephropathy at baseline

	Diabetes duration (years)					
Complication	**0-4**	**5-9**	**10-14**	**15-19**	**20-24**	**25+**
Microalbuminuria (%)	13.6	19.5	19.5	26.2	26.2	29.4
Macroalbuminuria (%)	4.4	7.4	7.4	12.5	12.5	16.1
End stage renal disease (%)	0	0	2	2	2	2

Macrovascular risk factors

The prevalence of macrovascular risk factors at baseline was based on data from AstraZeneca and includes the proportion of patients with cardiovascular events of all drug-treated patients with type 2 diabetes in Sweden. These values were used in the model estimations and is reported in Table A 4.

Table A 4 Prevalence of macrovascular events at baseline for men in different age intervals

	Age interval								
Risk factor	**18-39**	**40-50**	**51-55**	**56-60**	**61-65**	**66-70**	**71-75**	**76-80**	**81+**
Men									
Myocardial infarction (%)	0.5	3.0	5.5	7.3	8.8	10.4	12.0	13.8	17.9
Ischemic heart disease (%)	0.3	2.5	5.4	8.0	10.9	14.4	17.5	21.2	23.9
Stroke (%)	0.5	1.3	2.4	3.4	5.0	6.6	9.1	12.0	16.8
Heart failure (%)	0.7	1.6	2.7	3.6	5.1	6.8	9.9	14.2	22.8
Women									
Myocardial infarction (%)	0.1	1.2	2.3	2.8	3.7	4.6	6.1	7.5	11.5
Ischemic heart disease (%)	0.1	1.5	3.5	4.9	6.6	8.2	10.6	13.7	17.9
Stroke (%)	0.2	1.2	1.8	2.4	3.6	4.6	6.8	9.2	14.7
Heart failure (%)	0.2	0.9	1.6	1.8	2.7	4.2	6.6	10.6	21.1

Profiles of the incident population

For this study, we made the assumption that 33 000 people in Sweden are annually diagnosed with diabetes and that they have a similar risk profile to that reported by the NDR based on nearly 15 000 people with newly diagnosed diabetes [30]. We also divided the cohorts into a younger age group, with an average age of under 75 years, and an older age group, with an average age of 75 years and older. The number of people in each cohort in the younger age group and the respective age, gender, risk-profile and smoking status are presented in Table A 5.

Table A 5 Description of cohorts diagnosed with diabetes during one year (for the years 2013-2030), younger age group

Cohort	Age	Gender	Risk-profile	Smoker	Number
1	25	Female	High	No	36
2	25	Female	High	Yes	12
3	35	Female	Medium	No	180
4	35	Female	Medium	Yes	60
5	35	Female	High	No	147
6	35	Female	High	Yes	49
7	45	Female	Low	No	726
8	45	Female	Low	Yes	242
9	45	Female	Medium	No	508
10	45	Female	Medium	Yes	169
11	45	Female	High	No	218
12	45	Female	High	Yes	73
13	55	Female	Low	No	1 271
14	55	Female	Low	Yes	424
15	55	Female	Medium	No	889
16	55	Female	Medium	Yes	296
17	55	Female	High	No	381
18	55	Female	High	Yes	127
19	65	Female	Low	No	1 815
20	65	Female	Low	Yes	605
21	65	Female	Medium	No	1 271
22	65	Female	Medium	Yes	424
23	65	Female	High	No	545
24	65	Female	High	Yes	182
25	25	Male	High	No	54
26	25	Male	High	Yes	8
27	35	Male	Medium	No	265
28	35	Male	Medium	Yes	40
29	35	Male	High	No	217
30	35	Male	High	Yes	32
31	45	Male	Low	No	1 072

32	45	Male	Low	Yes	160
33	45	Male	Medium	No	750
34	45	Male	Medium	Yes	112
35	45	Male	High	No	322
36	45	Male	High	Yes	48
37	55	Male	Low	No	1 876
38	55	Male	Low	Yes	280
39	55	Male	Medium	No	1 313
40	55	Male	Medium	Yes	196
41	55	Male	High	No	563
42	55	Male	High	Yes	84
43	65	Male	Low	No	2 680
44	65	Male	Low	Yes	400
45	65	Male	Medium	No	1 876
46	65	Male	Medium	Yes	280
47	65	Male	High	No	804
48	65	Male	High	Yes	120
Total					**24 202**

The number of people in each cohort in the older age group and the respective age, gender, risk-profile and smoking status are presented in Table A 6.

Table A 6 Description of cohorts diagnosed with diabetes during one year (for the years 2013-2030), older age group

Cohort	Age	Gender	Risk-profile	Smoker	Number
25	75	Female	Low	No	1 089
26	75	Female	Low	Yes	363
27	75	Female	Medium	No	762
28	75	Female	Medium	Yes	254
29	75	Female	High	No	327
30	75	Female	High	Yes	109
31	85	Female	Low	No	359
32	85	Female	Low	Yes	120
33	85	Female	Medium	No	294
34	85	Female	Medium	Yes	98
35	95	Female	Low	No	73
36	95	Female	Low	Yes	24
61	75	Male	Low	No	1 608
62	75	Male	Low	Yes	240
63	75	Male	Medium	No	1 125
64	75	Male	Medium	Yes	168
65	75	Male	High	No	482
66	75	Male	High	Yes	72
67	85	Male	Low	No	531
68	85	Male	Low	Yes	79
69	85	Male	Medium	No	434
70	85	Male	Medium	Yes	65
71	95	Male	Low	No	107
72	95	Male	Low	Yes	16
Total					**8 799**

Risk factors incident cohorts

For the incident cohorts the risk factors are linked to the risk profile that belongs to the cohort; low, medium or high, and to gender. These risk factors are based on data from the NDR and are reported in Table A 7.

Table A 7 Three profiles of risk factors for men with newly diagnosed diabetes, baseline values

Risk factor	Risk-profile			Source
	Low	Medium	High	
Men				
HbA1c	6[a)]	6.9	8.65[b)]	Newly diagnosed NDR 2011 [30]
Systolic blood pressure (mm Hg)	125	135	140	[30]
Diastolic blood pressure (mm Hg)	80	80	90	Assumption
Total cholesterol (mmol/l)	5	5	5	NDR [31]
LDL-cholesterol (mmol/l)	2.1	3.1	4.1	NDR [31]
HDL-cholesterol (mmol/l)	1.5	1.31	1.24	NDR [31]
Triglycerides (mmol/l)	1.46	1.83	2.14	NDR [31]
BMI	25.1[c)]	30.7	36.3[d)]	Newly diagnosed NDR 2011 [30]
Women				
HbA1c	6[a)]	6.9	8.65[b)]	Newly diagnosed NDR 2011 [30]
Systolic blood pressure (mm Hg)	125	135	140	[30]
Diastolic blood pressure (mm Hg)	80	80	90	Assumption
Total cholesterol (mmol/l)	5	5	5	NDR [31]
LDL-cholesterol (mmol/l)	2.2	3.2	4.2	NDR [31]
HDL-cholesterol (mmol/l)	1.5	1.31	1.24	NDR [31]
Triglycerides (mmol/l)	1.46	1.83	2.14	NDR [31]
BMI	25.1[c)]	30.7	36.3[d)]	Newly diagnosed NDR 2011 [30]

a) Mean - 0,25 standard deviation, b) Mean + 0,5 standard deviation, c) Mean – 1,0 standard deviation, d) Mean + 1,0 standard deviation, NDR– Swedish National Diabetes Register, LDL–low density lipoprotein, HDL–high density lipoprotein.

For the younger cohorts, we assumed no presence of microvascular or macrovascular complications before diagnosis or at baseline, apart from nephropathy where we assumed the same values as for the prevalent cohorts with a diabetes duration of 0-4 years (Table A 3).

The older age group among the incident cohorts was assigned cardiovascular events that had occurred before diagnosis, in line with the older age group among the prevalent cohorts. These events were based on data from the NDR, where 6% was afflicted by ischemic heart disease, 3% by myocardial infarction, 5% by stroke, and 3% by heart failure before the diagnosis of diabetes [11]. Baseline values for diabetic retinopathy used for the prevalent cohorts were assigned the older age group among the incident cohorts (Table A 2). For nephropathy, the baseline values for cohorts with a diabetes duration of 0-4 years were used (Table A 3), and no prevalence of neuropathy was assumed at baseline. Prevalence of macrovascular complications at baseline for the older age group among the incident cohorts was assumed to be the same as for the prevalent cohorts in the same age (Table A 4).

Glucose lowering treatment

Treatment algorithms for the strategies SU/insulin and EASD/ADA are presented in Table A 8 to Table A 11 together with important treatment effects. Treatment costs, including costs of drugs, blood glucose measurement and medical visits, are reported in Table A 12.

Treatment algorithms and effects for cohorts younger than 75 years

Table A 8 Treatment effects: treatment strategy SU/insulin - cohorts younger than 75 years

	Treatment	Hba1c (mmol/mol) Threshold	HbA1c (mmol/mol) effect	SBP (mmHg) effect	BMI (kg/m^2) effect	Non-severe hypo[a)]	Severe hypo[a)]
	Non-pharmacological treatment at simulation start						
1	Non-pharmacological treatment	-	0	0	0	0	0
2	Met	60	-10	0	-0.1	0	0
3	Met + SU	60	-10	0.5	0.4	7	0.1
4	Met + NPH (20IE/day)	60	-5	0	1.7	5	0.1
5	Met + NPH (40IE/day)	70	-10	0	0	7	0.2
6	Met + NPH (20IE/day) + Mealtime (40IE/day)	70	-10	0	0	7	0.2
7	Met + NPH (30IE/day) + Mealtime (50IE/day)	70	-5	0	0	7	0.2
	Insulin at simulation start						
1	Met + NPH (20IE/day)	60	-5	0	1.7	5	0.1
2	Met + NPH (40IE/day)	70	-10	0	0	7	0.2
3	Met + NPH (20IE/day) + Mealtime (40IE/day)	70	-10	0	0	7	0.2
4	Met + NPH (30IE/day) + Mealtime (50IE/day)	70	-5	0	0	7	0.2

a) = Event rate of hypoglycemia at HbA1c level of 65 mmol/mol Met=metformin, SU=sulphonylurea, NPH=NPH-insulin, Mealtime = Mealtime insulin, SBP=systolic blood pressure, BMI=body mass index, hypo=hypoglycemia.

Table A 9 Treatment effects: treatment strategy EASD/ADA - cohorts younger than 75 years

	Treatment	Hba1c (mmol/mol) Threshold	HbA1c (mmol/mol) effect	SBP (mmHg) effect	BMI (kg/m^2) effect	Non-severe hypo[a)]	Severe hypo[a)]
	Non-pharmacological treatment at simulation start (70%)[b]						
1	Non-pharmacological treatment	-	0	0	0	0	0
2	Met	60	-10	0	-0.1	0	0
3	Met + DPP-4	60	-6	-2.4	-0.3	0	0
4	Met + DPP-4 + SGLT-2	60	-8	-3.3	-0.8	0	0
5	Met + SGLT-2 + NPH (40IE/day)	70	-10	0	0	7	0.2
6	Met+ NPH (30IE/day) + Mealtime (50IE/day)	70	-5	0	1.7	7	0.2
	Non-pharmacological treatment at simulation start (30%)[c]						
1	Non-pharmacological treatment	-	0	0	0	0	0
2	Met	60	-10	0	-0.1	0	0
3	Met + GLP-1	60	-12	-3.4	-1.0	0	0
4	Met + GLP-1 + NPH (20IE/day)	60	-5	0	0	7	0.2
5	Met + GLP-1 + NPH (40IE/day)	70	-10	0	0	7	0.2
6	Met + NPH (30IE/day) + Mealtime (50IE/day)	70	-5	0	1.7	7	0.2
	Insulin at simulation start						
1	Met + NPH (40IE/day)	-	-10	0	1.7	7	0.2
2	Met + SGLT-2 + NPH (40IE/day)	70	-10	-4.1	-0.8	7	0.2
3	Met + SGLT-2 + NPH (20IE/day) + Mealtime (40IE/day)	70	-10	0	0.4	7	0.2
4	Met + SGLT-2 + NPH (40IE/day) + Mealtime (60IE/day)	70	-10	0	0	7	0.2

a) = Rate of hypoglycemic events at HbA1c level of 65 mmol/mol, b = Treatment algorithm including DPP-4 and SGLT-2 used for 70% of the younger cohorts, c = Treatment algorithm including GLP-1 used for 30% of the younger cohorts, Met=metformin, DPP-4=dipeptidyl peptidase-4 inhibitor, SGLT-2= sodium/glucose cotransporter-2 inhibitor, NPH=NPH-insulin, Mealtime = Mealtime insulin, GLP-1= Glucagon-like peptide-1 agonist, SBP=systolic blood pressure, BMI=body mass index, hypo=hypoglycemia.

Treatment algorithms and effects for cohorts 75 years and older

Table A 10 Treatment effects: treatment strategy SU/insulin - cohorts 75 years and older

	Treatment	Hba1c (mmol/mol) Threshold	HbA1c (mmol/mol) effect	SBP (mmHg) effect	BMI (kg/m^2) effect	Non-severe hypo[a)]	Severe hypo[a)]
	Non-pharmacological treatment at simulation start						
1	Non-pharmacological treatment	-	0	0	0.2	0	0
2	Met	65	-10	0	-0.1	0	0
3	Met + SU	65	-10	0.5	0.4	7	0.1
4	Met + NPH (20IE/day)	75	-5	0	1.7	5	0.1
5	Met + NPH (40IE/day)	75	-10	0	0	7	0.2
6	Met + NPH (20IE/day) + Mealtime (40IE/day)	75	-10	0	0	7	0.2
7	Met + NPH (30IE/day) + Mealtime (50IE/day)	75	-5	0	0	7	0.2
	Insulin treatment at simulation start						
1	Met + NPH (20IE/day)	-	-5	0	1.7	5	0.1
2	Met + NPH (40IE/day)	75	-10	0	0	7	0.2
3	Met + NPH (20IE/day) + Mealtime (40IE/day)	75	-10	0	0	7	0.2
4	Met + NPH (30IE/day) + Mealtime (50IE/day)	75	-5	0	0	7	0.2

a) = Event rate of hypoglycemia at HbA1c level of 70 mmol/mol, Met=metformin, SU=sulphonylurea, NPH=NPH-insulin, Mealtime = Mealtime insulin, SBP=systolic blood pressure, BMI=body mass index, hypo=hypoglycemia.

Table A 11 Treatment effects: treatment strategy EASD/ADA - cohorts 75 years and older

	Treatment	Hba1c (mmol/mol) Threshold	HbA1c (mmol/mol) effect	SBP (mmHg) effect	BMI (kg/m^2) effect	Non-severe hypo[a)]	Severe hypo[a)]
	Non-pharmacological treatment at simulation start						
1	Non-pharmacological treatment	-	0	0	0.2	0	0
2	Met	65	-10	0	-0.1	0	0
3	Met + DPP-4	65	-6	-2.4	-0.3	0	0
4	Met + NPH (20IE/day)	75	-5	0	1.7	5	0.1
5	Met + NPH (40IE/day)	75	-10	0	0	7	0.2
6	Met + NPH (20IE/day) + Mealtime (40IE/day)	75	-10	0	0	7	0.2
7	Met + NPH (30IE/day) + Mealtime (50IE/day)	75	-5	0	0	7	0.2
	Insulin at simulation start						
1	Met + NPH (20IE/day)	-	-5	0	1.7	5	0.1
2	Met + NPH (40IE/day)	75	-10	0	0	7	0.2
3	Met + NPH (20IE/day) + Mealtime (40IE/day)	75	-10	0	0	7	0.2
4	Met + NPH (30IE/day) + Mealtime (50IE/day)	75	-5	0	0	7	0.2

a) = Event rate of hypoglycemia at HbA1c level of 70 mmol/mol Met=metformin, Met=metformin, DPP-4=dipeptidyl peptidase-4 inhibitor, NPH=NPH-insulin, Mealtime = Mealtime insulin, SBP=systolic blood pressure, BMI=body mass index, hypo=hypoglycemia.

Treatment costs

Table A 12 Treatment costs

Treatment	Yearly drug costs [a)]	Costs of blood glucose measurement [b)]	Costs of medical visits [c)]	Total costs
Non-pharmacological treatment	0	843	2 234	3 077
Met	724	843	2 234	3 801
Met + SU	1 510	843	2 234	4 587
Met + NPH (20IE/day)	1 840	6 409	2 234	10 483
Met + NPH (40IE/day)	2 955	6 409	2 234	11 598
Met + NPH (20IE/day) + Mealtime (40IE/day)	4 927	6 409	2 234	13 570
Met + NPH (30IE/day) + Mealtime (50IE/day)	6 257	6 409	2 234	14 900
Met + DPP-4	5 085	843	2 234	8 162
Met + DPP-4 + SGLT-2	11 063	843	2 234	14 140
Met + SGLT-2 + NPH (40IE/day)	8 933	6 409	2 234	17 576
Met + GLP-1	12 908	843	2 234	15 985
Met + GLP-1 + NPH (20IE/day)	14 023	6 409	2 234	22 666
Met + GLP-1 + NPH (40IE/day)	15 138	6 409	2 234	23 781
Met + SGLT-2 + NPH (20IE/day) + Mealtime (40IE/day)	10 905	6 409	2 234	19 548
Met + SGLT-2 + NPH (40IE/day) + Mealtime (60IE/day)	13 564	6 409	2 234	22 207

[a)] Reference: The price database of TLV 2016 [32], [b)] Self-measurement of blood glucose related to insulin therapy or not. Price reference: The price database of TLV 2013 [33], [c)] One visit at the doctors per year and one visit at the nurse every eighth month. Price reference: region Skåne 2013 [34]. Met=metformin, SU=sulphonylurea, NPH=NPH-insulin, DPP-4=dipeptidyl peptidase-4 inhibitor, SGLT-2= sodium/glucose cotransporter-2 inhibitor, GLP-1= Glucagon-like peptide-1 agonist.

Costs of complications

The costs used in the model for various complications of diabetes is presented in Table A 13 to Table A 16.

Table A 13 Costs of five types of diabetes retinopathy used in the model for the first and subsequent years. Swedish kronor (SEK), in the value of 2013

State of complication	Healthcare Resources, type and annual costs	Source
Background retinopathy	Eye Clinic Visits to the doctor normal fee: SEK 712 Screening image: SEK 427 Total cost first and subsequent years: SEK 1 139	[34]
Proliferative retinopathy	Eye Clinic Three doctor appointments normal fee: 3* SEK 712= SEK 2 136 Three doctor appointments with laser treatment including fluorescein angiography: 3*(SEK 1 993 and SEK 6 241) = SEK 24 702 Doctor appointments and screening images subsequent years Total costs first year: SEK 26 838 Total costs in subsequent years: SEK 1139	[34]
Macular edema	First year: three injections with ranibizumab 3*SEK 12 842= SEK 38 526 Subsequent years: 1 injection of ranibizumab SEK 12 842	[34]
Proliferative retinopathy & Macular edema	The other eye First year: three injections of ranibizumab 3*SEK 12 842= SEK 38 526 Subsequent years: 1 injection of ranibizumab SEK 12 842	[34]
Blindness	Literature review First year: SEK 8 610 a) Subsequent years: SEK 3 675 a)	[35]

[a)] Indexed to the latest year available, 2012, with the consumer price index, healthcare for sub-groups, from Statistics Sweden. Monthly index indicates marginal differences for 2013.

Table A 14 Costs of three types of diabetes nephropathy used in the model for the first and subsequent years. Swedish kronor (SEK), in the value of 2013

State of complication	Healthcare Resources, type and annual costs	Source
Microalbuminuria	Pharmaceutical treatment with angiotensin receptor blocker (50 mg losartan/8 mg candesartan) SEK 677 + calcium antagonist (5 mg) SEK 618 Total costs first year: SEK 648 Total costs subsequent years: SEK 1 295	[33]
Macroalbuminuria	Pharmaceutical treatment with • angiotensin receptor blocker (daily dose 50 mg losartan/8 mg candesartan) SEK 677 + calcium antagonist (daily dose 5 mg) SEK 618 • D-vitamin (2*500mg/day) SEK 1 312 3 control visits to physician (first year) 3*SEK 1386 = SEK 4 158 Total costs first year: SEK 6 765 Total costs subsequent years: SEK 2 607	[33, 34]
End-stage renal disease	KPP database E32 Dialysis SEK 124 584 317O Dialysis (outpatient) SEK 4 085 (3.5/week=> annual cost: SEK 743 470) Total costs first year: SEK 124 584 + 0.5*SEK 743 470[a)] = SEK 496 319 Total costs subsequent years: SEK 743 470	[36]

[a)] Patients in cohort may start dialysis anytime during a calendar year. On average, the first year of dialysis will therefore be 6 months long.

Table A 15 Costs of three types of diabetes neuropathy used in the model for the first and subsequent years. Swedish kronor (SEK), in the value of 2013

State of complication	Healthcare Resources, type and annual costs	Source
Symptomatic neuropathy	Pharmaceutical treatment for pain relief with gabapentin 3*800 mg per day SEK 11 746 Pharmaceutical treatment of erectile dysfunction (men only) 50 mg/week SEK 4 936 Total costs first year, men: SEK 8 341[a)] Total costs first year, women: SEK 5 873 [a)] Total costs subsequent years, men: SEK 16 684 Total costs subsequent years, women: SEK 11 746	[33, 37]
Peripheral vascular disease	Literature review Eurodiale results for ”Healed wounds” SEK 73 581 [b)] Risk of repeated wounds (assumption 10%) SEK 7 358 [b)] Total costs first year: SEK 73 581 Total costs subsequent years: SEK 7 358	[38]
Amputation	Literature review Eurodiale results for ”Major amputation” SEK 252 648 [b)] Risk of repeated wounds (assumption 10%) SEK 7 358 [b)] Total costs first year: SEK 252 648 Total costs subsequent years: SEK 7 358	[38]

[a)] Patients in cohort may start pharmaceutical treatment anytime during a calendar year. On average, the first year of pharmaceutical treatment will therefore be 6 months long.
[b)] Indexed to last available full year, 2012, using annual consumer price index, subgroup health care, at Statistics Sweden. Monthly indices indicate marginal differences for year 2013.

Table A 16 Costs of four types of macrovascular complications used in the model for the first and subsequent years. Swedish kronor (SEK), in the value of 2013

State of complication	Healthcare Resources, type and annual costs	Source
Myocardial infarction	Literature review Non-fatal first myocardial infarction: Total costs first year: SEK 79 921 [a)] Total costs subsequent years: SEK 1 708 [a)] Non-fatal second myocardial infarction: Total costs first year: SEK 80 716 [a)] Total costs subsequent years: SEK 1 708 [a)]	[39]
Stroke	Literature review Total costs first year: SEK 163 543 [a)] Total costs subsequent years: SEK 147 130 [a)]	[40]
Ischemic heart disease	Literature review Symptomatic ischemic heart disease: Total costs first year: SEK 94 251 [a)] Total costs subsequent years: SEK 3 394 [a)]	[39]
Heart failure	Literature review Heart failure: Total costs first year: SEK 62 852 [a)] Total costs subsequent years: SEK 4 812 [a)]	[39]

[a)] Indexed to last available full year, 2012, using annual consumer price index, subgroup health care, at Statistics Sweden. Monthly indices indicate marginal differences for year 2013.

Assumptions for hypoglycemic events

In the model, the user may specify two types of hypoglycemia: (1) non-severe and (2) severe, characterized by its annual frequency, impact on utility, health-care resource use and lost production. The costs are presented in Table A 17.

Table A 17 Costs per hypoglycemic event. In SEK 2013.

Type	Direct health care costs	Costs of lost production	Total costs	Source
Non-severe	22[a)]	34	56	[41]
Severe	1435[b)]	512	1947	[42]

[a)] Based on assumed frequency of health-care visits from reference [41] and the price of nurse visit in [34].
[b)] Frequency weighted average of three types of hypoglycemic events requiring assistance of other person (71%), from health care professional (28%), or hospitalization (1%).

Assumptions for loss of production for diabetic complications

Few data exist on the association between specific diabetic complications and loss of production. In the absence of published results, we made the following assumptions regarding relative loss of production compared to the average in the population by age and gender:

- −100% at end-stage renal disease;
- −50% at severe visual loss; lower extremity amputation (in current cycle); stroke (in current cycle); at second year and onwards after a second stroke; respectively;
- −25% at second year and onwards after lower extremity amputation; ischemic heart disease; all stages of myocardial infarction; in the second year after a stroke and until a subsequent stroke event; congestive heart failure; respectively.

The loss of production, and hence the indirect costs in absolute numbers, will thus depend age and gender of the cohort. All else equal, the costs of lost production for a given diabetic complication will be higher for a 40-year-old cohort compared to a 60-year-old cohort as the labor force participation in general is higher among 40-year-old people compared to 60-year-old people. Table A 18 shows age-specific expected annual salary adjusted for hours worked and labor force participation in Sweden year 2012 from Statistics Sweden; and annual costs of consumption based on [43] inflated to year 2012 using consumer price index. The salary and the costs of consumption are allowed to vary with age.

Table A 18 Expected salary based on annual full-time salary weighted for labor-market participation and average hours worked in the employed population age-group and annual costs of consumption inflated to year 2012.

Age interval (years)	Expected salary (SEK)[a)]
0-19	3 358
20-34	180 900
35-49	277 340
50-64	246 767
65-74	11 114
75-84	1 261
85+	206

[a)] Source: http://www.scb.se Monthly index indicates marginal differences for 2013.

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