Master Thesis Project

Medicine with Industrial Specialization – Medical Market Access

Department of Health Science and Technology

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Forord

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Cost utility analysis of second line treatment of T2DM in Denmark

Abstract

Background: In recent years the prevalence of T2DM has been increasing. However, little consensus continues to exist on the matter of second line pharmacological treatment. The analysis intends to investigate the cost-effectiveness of treatment with SU, DPP-4i and GLP-1 on a drug class level in order to provide clarity on the subject. More over, a focus is put on the risk of hypoglycemia and the effect of weight change, which have been central arguments in the debate of therapy choice.
Methods: A cost-utility analysis was carried out evaluating costs of therapy and quality of life associated with mild hypoglycemic incidences and weight change from pharmacological treatment of T2DM with DPP-4, SU and GLP-1, in a 1-year Danish treatment setting. Data on incidence of hypoglycemia and weight change was derived from a comparison of 17 randomized control trials. Cost of therapy was based on Danish pharmacy prices. A decision analytic model was constructed using TreeAgePro and one-way - and probabilistic sensitivity analyses were carried out using 10.000 simulations.
Results: In the base case analysis the cost of SU was 1427.59 Kr./year with an estimated 0,7734 QALY/patient. The DPP-4i had a cost of 5652,51 Kr./year with a value of 0,7871 QALY/patient. Finally the strategy of GLP-1 was 13052,18 Kr./year with 0,7944 QALY/patient. The SU proved most cost-effective type of therapy, however the result was sensitive to alterations WTP and QALY associated with weight change.
Conclusion: The analysis proved SU to be the most cost-effective choice of therapy at a WTP of 300.000 Kr. However, since the analysis only covers a 1-year treatment setting, long-term effects of especially SU should be taken into account. In addition it should be noted that no official Danish WTP exists and this parameter is important for the model-outcome.

Key words: Hypoglycemia, DPP-4 inhibitor, GLP-1 agonists, Sulphonylureas, Type 2 Diabetes Mellitus, Treatment algorithm.

Introduction

In recent years, the number of patients treated for type 2 diabetes mellitus (T2DM) in Denmark, has been increasing. 294.448 Danish patients were in 2012 diagnosed with T2DM, which is close to double the amount of patients with a T2DM diagnose in 2002.(1) Further, in Denmark it is estimated that 300.000 individuals suffer from undiagnosed T2DM and towards 750.000 are to be described as pre-diabetic. There are no signs leading towards a halt in the development of the increasing number of patients with T2DM and several prognoses suggest that there will be as much as 500.000 diagnosed T2DM-patients by 2020.(1-3) The amount and development of type 2 diabetes seen in Denmark reflects that of the world and by 2035 it is estimated that 592 mil. people worldwide will suffer from diabetes, 90 % of them T2DM.(4,5)

A similar trend is expected in the development of costs related to the treatment of diabetes and its complications(6) With several countries already spending large percentages of their total health care expenditures on diabetes, co-morbidities and treatment, the economic burden of the decease is substantial. (4,5,7) With no prospects of future change in the increasing prevalence together with the positive tendencies in mortality among diabetics, a substantial increase in expenses to diabetes treatment is expected.(8,9)

Treatment

In Denmark, treatment of T2DM is based on lifestyle intervention and pharmacological treatment. The patients are initially encouraged and offered support regarding dietary changes and increase of exercise often supplemented by relevant anti-diabetic medication. (10) In effort to

prevent cardio-vascular deceases and long term complications, an intensive poly pharmacological treatment of all risk factors is considered important, including lipid-lowering therapy, antihypertensive therapy, anti-hyperglycemic therapy and potentially anti thrombotic therapy.(10)

The effect of the hyperglycemic therapy is less clear, however tight glycemic control is considered a key factor in reducing development of diabetic complications.(11-13) The goal of an anti-diabetic treatment is to achieve a glycemic level as close to the normal non-diabetic level of glycated hemoglobin (HbA_{1c}) <6.5% without significant hypoglycemia.(10,11,13,14) As T2DM is a chronic and lifelong disease it is optimal to reduce the workload on the pancreas. Thereby aiding congested pancreatic ß-cells in utilizing any residual capacity of the cells to secrete insulin. Still it is generally considered difficult to avoid fatigue of the beta cells at some point during the patients life, though conclusive studies on the long term effect of DPP-4, GLP-1 and SGLT2 still remains.(15) The choice of anti-hyperglycemic agents is based on a treatment algorithm as well as considerations regarding health condition of the patient, safety profiles, tolerability, and expenses. While there is a broad consensus on the initial choice of treatment for T2DM being Metformine, the consensus of second line agents is less clear.(10,16) As a consequence practitioners are often left without a clear pathway of therapy to follow.(16)

The scenario of second line T2DM treatment is somewhat cluttered as there is little consensus on treatment strategy in a market with a wide range of therapy options. Further, little evidence exists on the issue of treatment order or the effect of combinations and benefits from the individual products constituting the major drug classes. With the intention of developing a decision model in mind, the following will describe the effect and role of the different types of therapy options on a drug class level in an attempt to clarify matters of the second line treatment algorithm for T2DM. More over, a focus is put on the risk of hypoglycemia and the effect of weight change, which have been central arguments in the debate and choice of therapy.

Algorithm

The treatment algorithm consists of Sulphonylureas (SU), DPP-4 inhibitors, GLP-1 agonists, SGLT2 inhibitors and insulin each with a range of recommendations. Insulin as a second line treatment is only recommended in cases where intensive treatment is necessary.(10) On this basis this drug class is not incorporated into a decision model.

The SGLT2-inhibitors belong to a relatively new class of agents, and have in clinical studies proved highly effective in reducing HbA_{1c}-levels. In addition, SGLT2-inhibitors also lower blood pressure as well as they induce a significant weight reduction, and do not involve risk of hypoglycemia. In turn, there is seen a relatively high risk of urinary tract infections (30%) and the long-term consequences are yet unknown. (15,17) The SGLT2-inhibitors have not yet gained broad application in Denmark and were just recently added to the treatment algorithm. For this reason together with not inducing hypoglycemia, SGLT2-inhibitors are not incorporated into the decision model.

Sulphonylureas

SU's were the first oral glucose-lowering therapy to be introduced in clinical practice around 1958. (17,18) The first generations of SU were effective but were associated with high risk of adverse events. More recently generations of the SU products have an optimized tolerability profile. (17) Recently, the use of SU has been declining due to other therapy alternatives and today approximately 25 % of patients receive SU in the treatment of T2DM in Denmark.(19) The SU are known for their fast onset of effect together with a low price, currently between 100-2000 Kr. for 1 year of therapy.(20) SU's are typically administered orally twice daily and work by blocking ATP-sensitive potassium channels in the pancreatic ß-cells, stimulating secretion of insulin. Functional ß-cells are essential to achieve an effect from SU treatment. SU's are effective in reducing HbA_{1c} levels by approximately 1-2 %-points but are contraindicated in severe kidney and liver disorders. (17,18,21) On the risk-balance, studies report a risk of hypoglycemia of up to 36 % and a weight gain of up to 2 Kg. (21,22)

Several studies have demonstrated a decline in the SU's effect on HbA_{1c} after 6 months of treatment because of increased ß-cell dysfunction. Other studies report an increase of the risk of cardiovascular disorders. (16,21) Due to the high risk of hypoglycemia SU's are generally not recommended in the treatment of elderly who are living alone, commercial drivers, scaffolders, patients with an alcohol abuse, or who suffer from severe renal impairment.(10)

GLP-1

Glucagon Like Peptid-1-receptor-agonists / mimetics (GLP-1) is a more recently developed type of antidiabetic therapy. Thus, Byetta (exenatide / Eli Lilly) was approved for marketing by The European Commission in the European Union on 20 November 2006. Later, Victoza (liraglutide / Novo Nordisk) was approved in June 2009, and most recently Lyxumia (lixisenatide / Sanofi Aventis) was approved February 2013. The drug class has proven very effective and reduces HbA_{1c} levels between 0.9-1.9 % while additionally inducing a weight loss in the range of 5.5 Kg in adipose diabetics. (17,21) GLP-1-based therapy works by activating GLP-1 receptors throughout the body and inducing an increased secretion of insulin from pancreatic ß-cells together with suppression of glucagon secretion by pancreatic α-cells. (17,23) GLP-1 agonist also contribute to stable blood sugar levels by delaying gastric emptying, reducing central appetite, and studies have shown that GLP-1 agonists may even increase ß-cell mass and function. (23-25) The most common side effects in the treatment with GLP-1 are nausea, vomiting and diarrhea, which are seen in about 50 % of patients. Hypoglycemia is less frequent and is experienced by approximately 5 % of patients. GLP-1 agonists are contra indicated in patients with kidney disorders and pancreatitis. (10,17,21) GLP-1 agonists are administered by subcutaneous injections in a long acting (bydureon / exenatide) and short acting versions (victoza, lyxumia) once weekly or twice daily, respectively. (17,23) Currently, approximately 10 % of Danish T2DM patients are treated with a GLP-1 based treatment. (19) The cost of GLP-1 treatment is relatively high and it is obviously a market with few actors currently. The cost of exenatide is 9.300 Kr./year. With a market share of approximately 2 % and Liraglutide with a price of 12.600 Kr. and a market share of approximately 98 %.(20,26) On the basis of the relatively high price of GLP-1 treatment, the reimbursement status of this therapy was by September 2013 adjusted to conditionally reimbursement by the Danish Health and Medicines Authority. (27)

DPP-4 Inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4i) belong to a class of anti-diabetics introduced to Danish market for the first time in 2006 (Januvia (sitagliptin) / MSD). (17) The DPP-4i treatment results in a moderate effect on HbA_{1c} levels reducing it with 0.4-1.4 % but is generally well tolerated. (17,21) The DPP-4i drug works by inhibiting the DPP-4 enzyme, which causes break down of the incretin hormones, GLP-1 and Glucose dependent insolinotropic polypeptid (GIP). Both incretin hormones, GLP-1 and GLP stimulate the insulin secretion from the pancreatic ß-cells and the effect depends on ingestion of a meal, which stimulate the gut to secrete the incretin hormones. Additionally, GLP-1 also suppresses secretion of glucagon from pancreatic α-cells. DPP-4i therapy is very well tolerated. Thus, adverse events are rare, resembling that of placebo. (17,28) Hypoglycemia has been reported to occur minimally in approximately 3-5% of patients. The DPP-4i drugs may induce a slight weight loss, but are generally considered weight neutral. (21) All DPP-4 inhibitors marketed so far (sita-, vilda-, saxa-, and alogliptin) are mainly eliminated via the renal route, but not Linagliptin, which is eliminated with faeces, and must therefore be dose-reduced in patients with moderate to severe kidney disorders.(17) DPP-4i are typically administered orally once a day, twice in combination with metformin, and the cost of 1-year therapy ranges from 4100-5800 Kr.(20) Currently approximately 13 % of diagnosed Danish T2DM patient are treated with DPP-4i in combination with Metformine.(19)

Adverse events

Hypoglycemia

In glucose reducing therapy in the treatment of T2DM, hypoglycemia is often seen as a frequent and serious side effect, which can occur anytime during day or night. (29) Hypoglycemia occurs when blood

glucose falls to levels below the normal physiological range and symptoms include shakiness, irritability, sweating, anxiety, confusion, disorientation, dizziness and in severe cases seizures and loss of consciousness. (29-31) Classification of severity of hypoglycemia is inconsistent but is often categorized as mild/moderate/severe. Mild episodes are typically defined as patients experiencing low blood glucose levels but without the requirement of external assistance to recover. Conversely moderate episodes require the assistance of other people and severe episodes leads to hospitalization. (12,32). Strict glycemic control has been proven to reduce the risk of cardiovascular complications, however resent studies suggest an increased morbidity and quality of life in elderly patients.(33)

Weight change

T2DM is associated with overweight and consequently lifestyle changes and weight control is a key point in the treatment of T2DM. Besides the physical health challenges from overweight it is also connected to reduced quality of life (QoL). (34,35) Several current products for treatment of T2DM effects the body weight and weight change are taken into consideration in the choice of therapy.(10)

Quality of Life

Hypoglycemia has a major impact on patient lives in terms of physical, mental, and social functioning and patients can experience impaired work function by even mild hypoglycemic events**.** (29,36) Hypoglycemia is connected to reduced quality of life and limitation for the patient and is often associated as a major barrier to adequate management of diabetes.(12) To avoid hypoglycemia patients may intentionally avoid exercise, overeat or reduce the amount of medication taken, there by challenging treatment compliance and complicate glycemic control**.**(29,37,38)

Several studies have also found that fear of hypoglycemia is associated with a significant decrease in quality of life. (32,35) More over fear of hypoglycemia can result in reduced work and physical exercise together with increased risk of long term complications from diabetes if glucose levels are not maintained. (32,37,39) For T2DM patients treated with anti diabetics the extent of reduced QoL increases with frequency of episodes and severity. (37) In this context patient specific factors that impact health-related quality of life are becoming increasingly important in achieving the optimal diabetes treatment.(40)

Objective and definition

As resources are scarce in the healthcare system an optimal allocation of resources should be sought. This is particularly relevant in treatment areas where spending is increasing and treatment scenarios unclear.

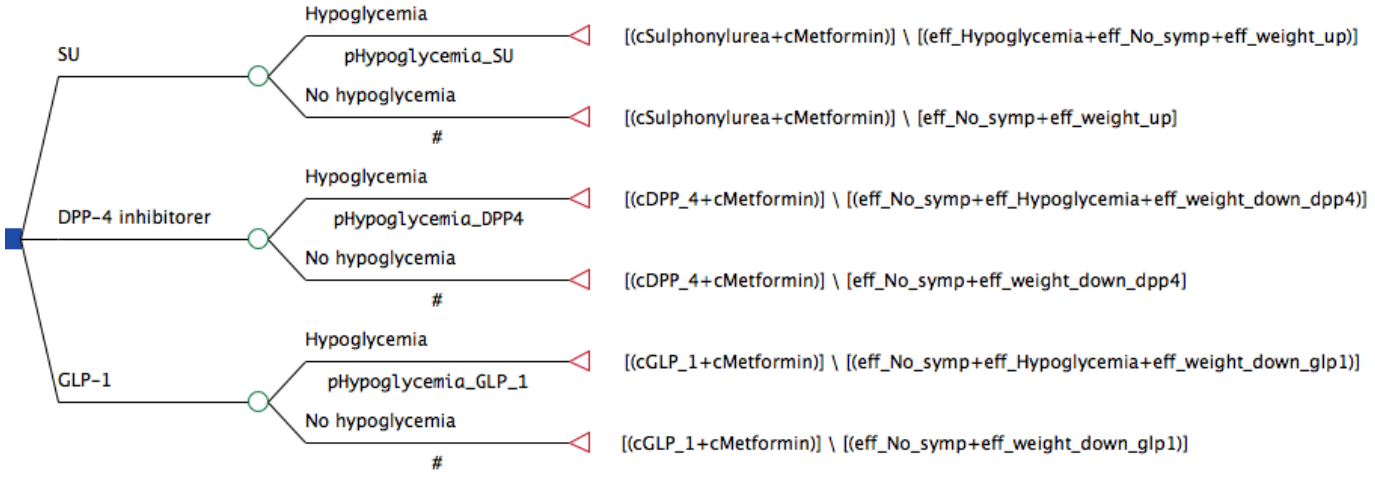
The purpose of this analysis is to perform a health economic evaluation of the market for second line therapy for T2DM. The analysis intends to investigate the cost-effectiveness of treatment with SU, DPP-4i and GLP-1 on a drug class level. A cost-utility analysis is carried out evaluating costs of therapy and quality of life associated with mild hypoglycemic incidences and weight change from pharmacological treatment of T2DM, in a 1-year Danish treatment setting.

Methodology

Decision Tree

To evaluate the cost and effectiveness of current second line pharmacological treatment of T2DM a decision analytic model was designed using the Software TreeAge Pro 2014®. The model was designed as a decision tree with 3 branches, assigned the average cost of a 1-year treatment with SU, DPP-4i and GLP-1, respectively. Each of the branches representing one treatment strategy, were further divided into two additional branches based on the probability of hypoglycemic events occurring. One branch represents the scenario of hypoglycemia the other a scenario of no hypoglycemia and both ended with a terminal node. Each of the two scenarios was assigned probabilities and values of QALY for hypoglycemia and weight change. The simulation of the decision tree was performed and cost effectiveness charts were derived.

Figure 1: Illustration of the decision tree constructed in TreeAgePro ®. Each type of therapy branches in to the either the possibility of hypoglycemia or No hypoglycemia. A probability is assigned each branch and at the rectangular end nodes values associated with the outcome are assigned the given branch. The exact value can be seen in Table 1.



Search methodology

A search on PubMed was conducted to retrieve available literature regarding hypoglycemia and T2DM, adverse events associated with GLP-1, DPP-4i and SU's. The research was performed between February and may 2014 with no date limit applied, using combinations of several search terms including: hypoglycaemia, hypoglycemia, type 2 diabetes mellitus, glycemic control, quality of life, utility, EQ-5D, DPP-4 inhibitors, GLP-1 agonist, sulphonylureas, insulin, SGLT2, weight change, cardio vascular risk, Liraglutid, Exenatid, Glipizide, Gliclazide, Glimepiride, sita-, vilda-, saxa- and linagliptin. All search terms were combined with the terms review, meta-analysis and all abbreviations were written out. Studies reporting on prevalence of hypoglycemia in the treatment of T2DM and its impact on quality of life were reviewed and selected based on relevant and comparable data. Only studies in English language were included.

As a consequence of inconsistencies in the literature regarding probabilities of achieving hypoglycemia, its impact on quality of life and weight change, a coarse comparison of several studies were conducted. The comparative analysis was performed in a systematic manner but does not meet applicable requirements of fulfillments of systematic reviews or meta-analysis.

Probabilities of hypoglycemia and weight change

Through the literature research a total of 21 studies reporting on weight change and probability of hypoglycemia from anti diabetics discussed in this article were found. Data was retrieved from 10 studies on DPP-4i (22,41-49), 5 studies on SU(22,41,43,50,51), and 5 studies on GLP-1(42,52-55). The majority of the studies were double-blinded randomized control trials with duration of 12-104 weeks. All studies shared same definition of mild hypoglycemia and all studies were conducted between 2005-2012 and 19 studies involved more than 200 participants. For each drug class, the obtained probabilities of hypoglycemia as well as data on weight change were summed weighted after population size and a mean was calculated (see table 1). Only studies carried out on drug naïve patients or patients in Metformine treatment were used. In addition the mean BMI of GLP-1, DPP-4 and SU patients were 32.8, 30.8 and 30.6, respectively.

Quality adjusted life years

Several studies have been conducted to investigate the effect of hypoglycemia on quality of life. On the basis of differences in study designs and evaluation of utility, 4 studies were selected based on comparability. The studies selected all reported utility scores by severity, graded as: none, mild, moderate and server, using the EQ-5D index. By

adding the utility scores from each individual study a mean for severity grade was calculated. A weighing of the reported utilities was done by assigning each of the utility values the percentage of the study population constituted of the total population in the 4 studies.

Table 1 - Assumptions regarding model parameters

Costs	**Kr.**
DPP-4i	5309.41
GLP-1	12709.08
Sulphonylureas	1048.48
Metformine	343.10
Probability of hypoglycemia	**%**
DPP-4i	0.033
GLP-1	0.067
Sulphonylureas	0.255
Effect	**QALY**
Hypoglycemia	-0.0336
T2DM with no symptoms	0.7859
Weight loss DPP-4	0.0023
Weight loss GLP-1	0.0107
Weight gain SU	-0.0039

QALY's for weight change

From the same studies used to derive the risk of hypoglycemia, data on weight and BMI of the study population was derived. A mean for weight and BMI was calculated for each drug class. The mean weight change for each drug class was then used to calculate new BMI's for GLP-1, DPP-4 an SU. A value for the difference in the BMI before and after therapy was found and multiplied by 0.01 QALY the value of a 1 unit change in BMI**.** The effect of weight change for GLP-1, DPP-4 and SU used in the model were 0.0107 QALY, 0.0023 QALY and 0,0039 QALY, respectively.

Cost of therapy

The pharmaceutical products used in this analysis are based on the Danish algorithm of treatment. Within each drug class of GLP-1, DPP-4 and SU, individual products from different manufactures together with their market shares were identified and data retrieved.(26) Prices used in the model were derived from the Danish Health and Medicines Authority and are based on the lowest indicated price pr. defined daily dose (DDD) multiplied by 365**.** (20,56) In absence of DDD listing for some products, the lowest price pr. unit was multiplied by the dosage proposal announced on promedicin.dk and multiplied by 365 days. The mean of prices in each drug class were calculated and adjusted for market share by assigning market percentages to the individual product prices. The price of Metformine is exclusively based on the least costly product listed on medicinpriser.dk. All costs are presented in 2014 Danish Kroner (May 12th 2014).

Sensitivity analysis

One-way sensitivity analysis

One-way sensitivity analyses were performed, in which parameters were varied one by one to evaluate their isolated impact on the model outcome. The values used were the highest and lowest estimates, derived from the literature. Thus, the outlying estimates for the parameters for QALY, risk of hypoglycemia, cost of drug classes and weight change were applied to the model. Furthermore, a series of threshold analyses were performed to investigate at what limit value the model outcome would change.

Probabilistic sensitivity analysis

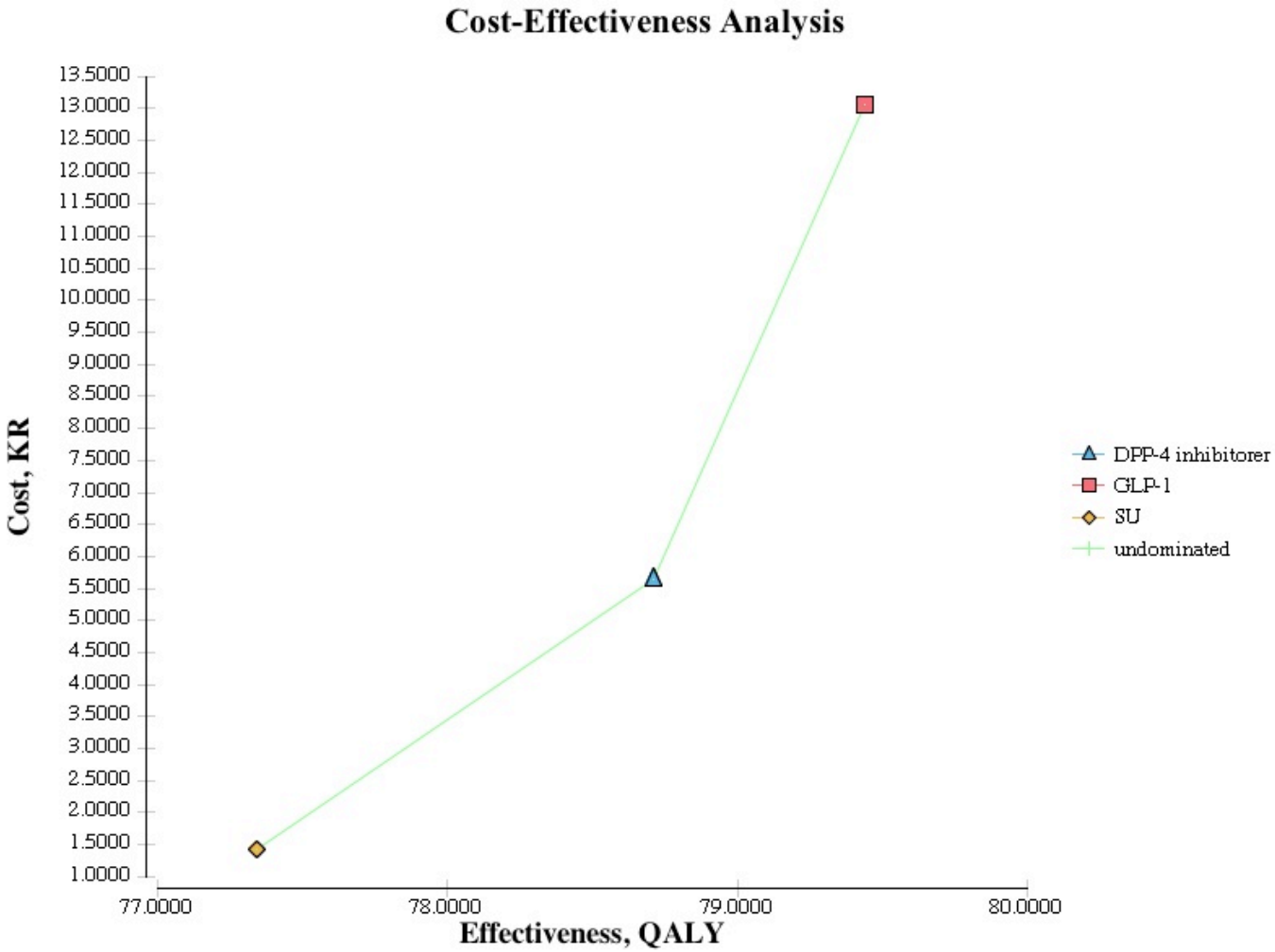
In order to perform probabilistic sensitivity analysis, standard deviations were calculated for parameters used in the model and entered in TreeAge Pro® which was used to perform the calculations. Except QALY-values for weight change and the price of Metformine, all parameters were assigned weighted means and standard deviations. All standard deviations applied were normal distributed. Parameters representing probabilities of hypoglycemia were assigned ß- and α-distributions. A Monte Carlo simulation was performed with 10.000 simulations and cost-effectiveness acceptability curves were derived.

Results

The base case

The initial results, of simulating the cost utility model without distributions, shows a cost of 1427.59 Kr. of the SU strategy weighted for probabilities of hypoglycemia occurring with an estimated QALY per patient of 0,7734 QALY. The DPP-4 strategy is associated with costs of 5652,51 Kr. with an effectiveness of 0,7871 QALY's. The DPP-4 strategy is thereby more effective but also more expensive than the SU strategy. More over the DPP-4 strategy have an ICER of 308498,96 Kr. And finally the strategy of GLP-1 is estimated to a cost of 13052,18 Kr. and 0,7944 QALY's. The GLP-1 strategy is more effective than DPP-4 and SU but also more expensive with an ICER of 1,014,309,91 Kr.

Figure 2: *Cost effectiveness chart of SU, GLP-1 and DPP-4 in a 1-year treatment of T2DM. The effectiveness is measured in QALY and the cost in Danish Kroner. As seen, the SU therapy results in an expected value for price of 1427.59 Kr and 0,7734 QALY. DPP-4, costs 5652.51 Kr/0,7871 QALY. The GLP-1 strategy is 13052,18 Kr./0,7839 QALY, thereby being more effective and but also more costly than treatment with DPP-4 and SU.*



One-way sensitivity analysis

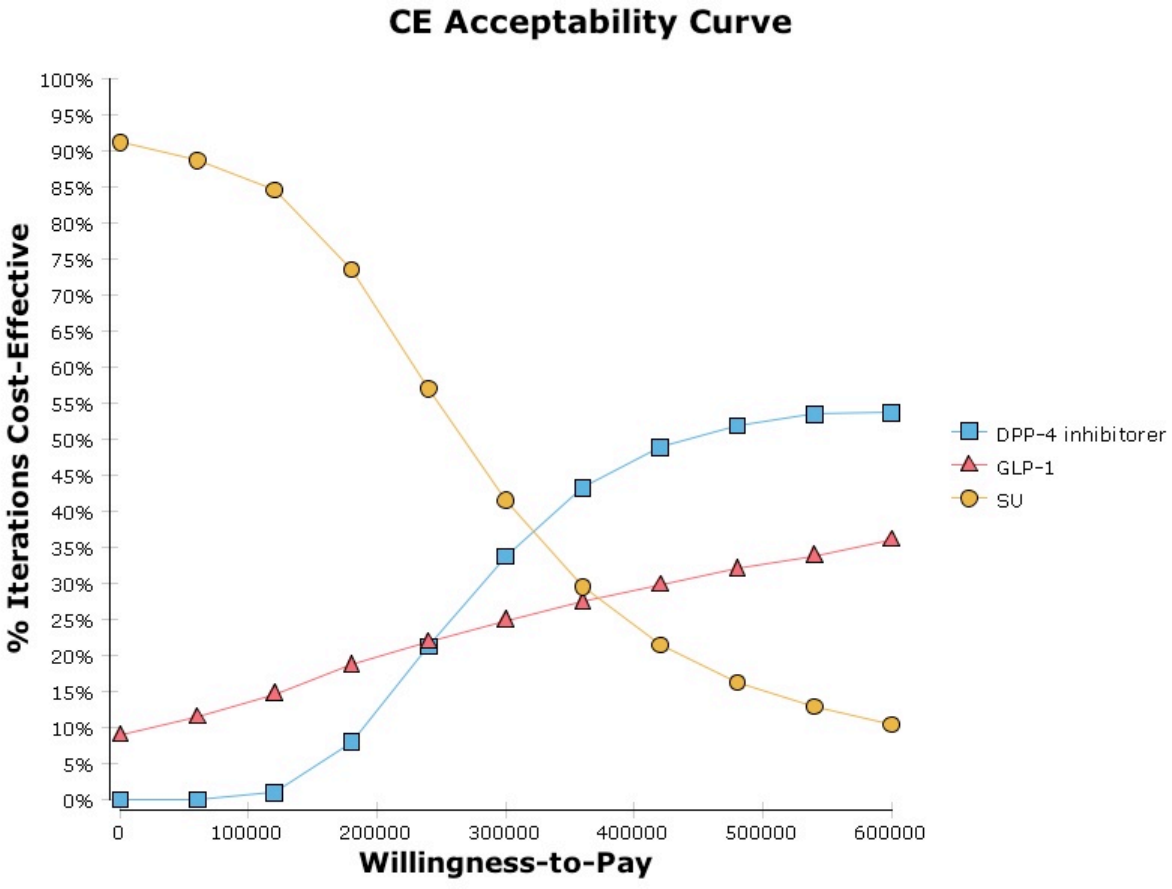
The sensitivity analyses showed that alteration of variables had little effect on the outcome of the base case analysis. Altering prices changed the cost-effectiveness of the individual drug class but not on the base case outcome. Increasing the effect of hypoglycemia causes DPP-4 and GLP-1 to become more cost-effective. If the QALY impact from suffering from hypoglycemia is greater than -0,25 QALY the outcome of the decision model changes and DPP-4 becomes the recommended treatment. Changing the QALY's associated with weight change had some effect on the model. If QALY gained from loosing weight with DPP-4 treatment exceeds 0.00271 the result of the base case would turn out in favor of DPP-4 therapy. This is interesting since the outliers range from 0,0057-0,001, with and average of 0.002317 QALY's. If therapy with SU would cause a QALY loss greater than 0.00432

QALY from weigh gain a similar result would happen and DPP-4 become the preferred treatment strategy. The effects of SU on QALY due to weight gain range from the outlying values of -0.00478-0.00209 QALY. Alteration of values for weight change from therapy with GLP-1 had little effect on the outcome of the base case analysis. Varying probability values of hypoglycemia within the range found in the literature did not change the outcome of the model.

Probabilistic sensitivity analysis

The results of the 10.000 Monte Carlo simulations are presented in a cost-effectiveness acceptability curve in figure X. Here the relations between the three treatment options are depicted on a graph showing the willingness to pay in relation to the percentages of iterations for which each option is cost-effective. The results show that SU have the highest probability (43 %) of being the most cost-effecting choice of therapy at a WTP of 300.000 Kr. compared to DPP-4 (35 %) and GLP-1 (24 %). Further, as the WTP increases the probability of GLP-1 and DPP-4 being cost-effective rises. At a WTP greater than 320.000 Kr. DPP-4 have the highest probability (37,66%) of being the most cost-effective choice of therapy in comparison with SU (37,17 %) and GLP-1 (25.17 %). The threshold for GLP-1 to become the most cost-effective choice is at a WTP level of 983.600 Kr.

Figure 3: Cost-effectiveness acceptability curve. As depicted SU therapy is the most cost-effective choice of therapy at a WTP of 300.000 Kr. As the WTP increases so does the cost-effectiveness of DPP-4 and GLP-1.



Discussion

The result of the analysis showed that SU are the most cost effective product in the treatment of T2DM in a Danish setting at a WTP of 300.000 Kr. But since there is no official WTP threshold in Denmark a slightly higher WTP of 320.000 Kr. could change the decision to favor DPP-4 therapy. Further, the results show GLP-1 as the most efficient anti-diabetic but at a much higher cost and a cost-effectiveness threshold of 983.600 Kr. Alterations of the parameters for probability of hypoglycemia or the product prices do not seem to affect the model outcome. However some sensitivity is seen in the parameters of weight change and QALY estimates and it is important to note than even small changes to the effect of weight could change the model outcome.

Limitations

The primary limitation of this study was the availability and consistency of data. On this basis a coarse comparison of gathered data was conducted, but without living up to accepted standards for meta-analyzes. In addition, there are several parameters the model does not take into account in terms of pharmacological treatment of T2DM. Among others, the route of administration, additional side effects and their impact on compliance and QoL, besides the importance of the glycemic control.

A significant generalization is carried out when comparing a wide variety of products in drug class level, since products to some extent differ in the way of function or administration. However, there is agreement on certain uniformity and several studies in the literature evaluate second-line treatment of drug class levels. Another limitation is the static depiction of product prices, which are constantly changing especially for SU, which are off patent. More over prices used are weighted after product market shares that can equally vary. Product costs are based on pharmacy prices and does not consider the possibility of volume discount, however the majority of T2DM patients are part of the primary sector, not affected by public procurement schemes.

As seen in the sensitivity analysis the parameter of weight change was of importance to the model outcome. In this study, the extend of weight change was estimated to range between a loss of 3.5 Kg to a gain of 2 Kg depending on therapy. A weight change of this magnitude can be described as minor taken the average BMI of T2DM patients into consideration and the effect on QoL or the physical state of health may be arguable. However some studies report clinical importance of even minor weight changes.

The overall estimations of QALY's for T2DM patients used to evaluate impact of weight change and hypoglycemia are vague. Though several studies report on the subject they differ in methods, measure scale and results vary. Yet, common to all studies on the matter, they do report a significant effect on QoL from even mild hypoglycemic incidences.

In the probabilistic sensitivity analysis standard deviations were applied to the parameters. It can be argued that the use of standard error would have been more correct. But as standard deviations involve greater values and thus greater variance it was applied to reflect the uncertainties and deviances of the model parameters.

The purpose of a decision-model is to aid in the decision process by simulating different scenarios depicting reality. Limitations in the model-construction of this study, includes not considering time or allowing the possibility for changing between different treatment scenarios. As a consequence important consequences regarding SU are not taken into consideration. The fact that SU can induce fatigue of the pancreas within few years of treatment, leading to the necessity of insulin treatment would affect the cost-effectiveness of SU. As treatment with insulin is more expensive, associated with substantial side effects and thus lower quality of life, the depiction of treatment with SU is not complete.

On this basis a Markov model could in future studies be recommended to conduct a more realistic simulation of treatment scenarios by including a time factor. But this case would make great demands to quality and availability of data.

A point of consensus is the effects and importance of the reduction of HbA_{1c} levels in T2DM patients. But recent studies have challenged this perception, indicating an increased mortality in patients with

strict glycemic control together with reduced QoL. (33) More over T2DM patients are generally of older age and many suffer from more than one chronic illness. (57,58) On this basis QoL might be of higher priority than clinical efficiency to certain groups of patients.

Overall a decision model is not better than the information you put in to it and one of the key limitations of this model is the quality and availability of data. In this case, consistent data on QoL have been scarce, as only few studies have investigated the impact of weight change, mild hypoglycemic incidences or the condition of non-symptomatic T2DM on QoL. Further more, data from literature on hypoglycemic risks of all therapy types were cluttered and without consensus. Although, parameters mentioned above still constitute a key role in choosing the right therapy.

In this analysis SU turns out as the most cost-effective therapy as second line treatment of T2DM in a Danish setting. But a major limitation of the study is the neglect of time span and the long-term effect of SU on pancreatic ß-cells and should be taken into consideration. Leaving SU out of the consideration and assuming a willingness to pay of 300.000 Kr. DPP-4i would be come the most cost-effective choice in comparison to GLP-1. As of November 11th 2013 GLP-1 have been withdrawn from general reimbursement, leaving a distinct value for WTP a key point in deciding the most cost-effective option of DPP-4 or SU's. In turn, as GLP-1 being the most effective product any reduction of price would enhance its cost-effectiveness.

Further Research

Further studies should be carried out to clarify the matter of second line T2DM treatment in favor of the patients together with the health economic considerations, since T2DM accounts for an increasing and substantial health risk and expense to society. Research should aim to clarify the effect of hypoglycemia and weight change on QoL together with existing evidence on the probability of achieving mild hypoglycemic incidences from second line T2DM therapy. Transitional probabilities among therapy types should be clarified in order to conduct a CUA using a Markov-model and more over, costs and probabilities of other adverse events from second line treatment would be interesting to incorporate. Further more, a recent study have been evaluating the effect of hypoglycemia on work productivity, yet another parameter that would enhance the depiction of the treatment scenario additionally.(59)

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