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Title: Non-brand specific cost-effectiveness analysis of using GLP-1 agonists in combination with basal insulin in Denmark

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Resume:

Background: GLP-1 agonists have shown great promise in reduction of blood glucose and weight without increasing the risk for hypoglycemia in type 2 diabetes patients uncontrolled on previous treatment with basal insulin and metformin.
Objective: A non-brand specific cost-effectiveness analysis was undertaken to investigate whether the addition of a GLP-1 agonist to basal insulin + metformin was cost-effectiveness compared to basal insulin + metformin in a Danish setting.
Method: A meta-analysis was undertaken of two trials which both compared basal insulin + GLP-1 agonist with basal insulin + placebo. The combined outcome was used as input in the cost-effectiveness analysis performed in the IMS CORE Diabetes model. The time frame of the analysis was 50 years.
Results: The cost-effectiveness analysis showed that treating type 2 diabetes patients uncontrolled on basal insulin + metformin with the addition of a GLP-1 agonist was associated with an estimated incremental cost-effectiveness ratio of 564333 DKK per quality-adjusted life year compared to treating with basal insulin + placebo.
The studies used in the analysis showed conflicting outcomes, which affected the result of the analysis.
Conclusion: Further research is needed in order make a final conclusion.

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Bilagsantal: 12
Sideantal: 55

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PREFACE

Diabetes is great burden for the individual patient and to the society. In the last decade the pharmaceutical development in antihyperglycemic compounds opens for new and interesting treatment options for patients, which is currently in poor control. One of these compounds is the glucagon-like peptide-1 (GLP-1) agonists, which have been shown to induce a decrease of the blood glucose and weight without severe adverse events. Addition of a GLP-1 agonist to a treatment regiment of basal insulin has shown improved glycemic control but is the treatment costs-effective in a Danish setting. In order to investigate this a cost-effectiveness analysis was undertaken using the widely used diabetes specific model: IMS CORE Diabetes model.

DIABETES MELLITUS – A GLOBAL EPIDEMIC

Diabetes mellitus is one of the most widespread non-communicable disorders across the globe and the prevalence has been increasing during the last decades with a worrying rate. In 2013 the International Diabetes Federation (IDF) estimated the prevalence in 219 countries to be 381.8 million adults living with diabetes, and the projected estimation for 2035 to be 591.9 million(1). Because of these estimates diabetes are now widely recognized as a global epidemic(2). Seen from a Danish perspective diabetes is likewise a increasing healthcare concern as *Carstensen and colleagues*(3) reported in 2008: based on the national diabetes registry a prevalence of 230.000 or roughly 4.2% of the entire Danish population in 2007(3). The increasing number of diabetic patients needing treatment results in an increasing burden on the healthcare system. Furthermore, a large proportion of patients and physicians are hesitant to initiate or intensify the needed insulin treatment in a timely manner to fit the progress of the disease. This hesitation is due to fear of weight gain and hypoglycemia that is associated with insulin treatment, which results in inadequate glycemic control and subsequent increased cost to the society and healthcare system(1,3-5).
Consequently new treatments are needed to diminish the effects of insulin and improve the patient adherence to the glucose lowering therapy(6).

Diabetes Mellitus

Diabetes mellitus is a chronic metabolic disorder affecting the carbohydrate, fat and protein metabolism as a consequence of declining insulin secretion resulting in an increased blood glucose or hyperglycemia. Hyperglycemia is associated with a number of microvascular and macrovascular complications, which affect the quality of life and increase the mortality rate compared to non-diabetic populations. Diabetes mellitus is a heterogeneous disorder with a large degree of variation in the underlying pathological mechanism causing the disorder, thus making a classification of the disorder difficult. The classification of diabetes mellitus is divided into four main categories: Type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), other types of diabetes mellitus and gestational diabetes mellitus (GDM)(7). The scope of this research is type 2 diabetes therefore no further elaborating will be done of the other types.

Normal Glucose Homeostasis

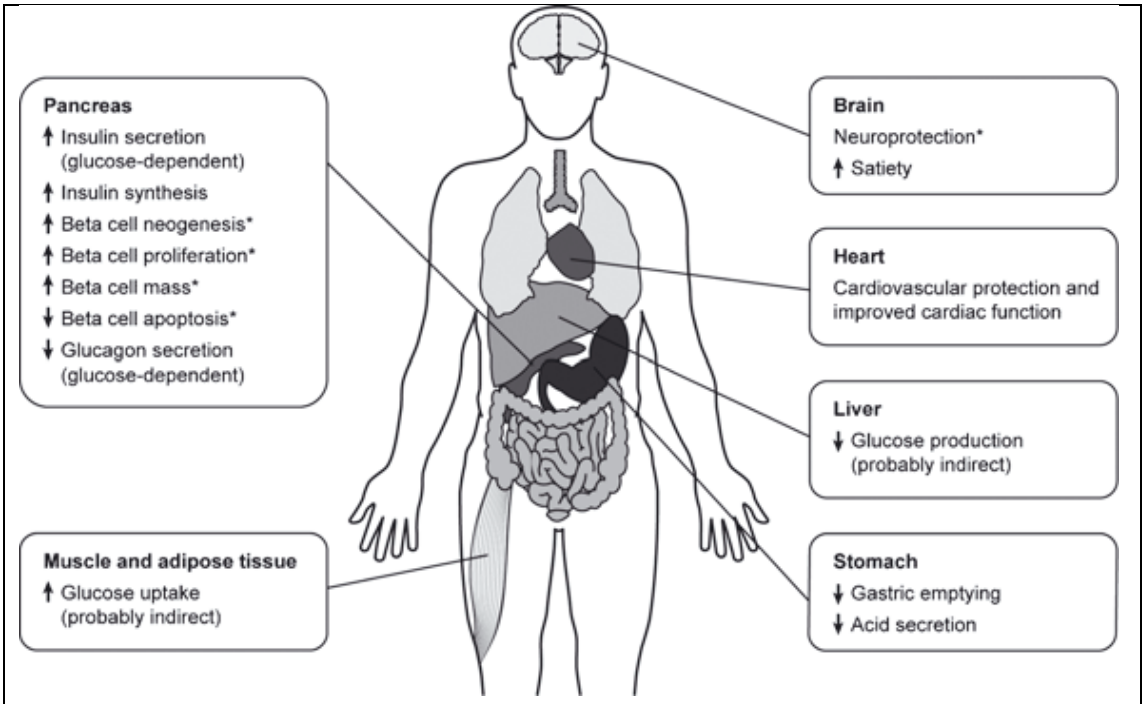
Diabetes mellitus occurs when the normal glucose regulation is malfunctioning. Maintaining a stable level of glucose in the circulation is complex and affected by multiple factors that regulate the uptake and removal of glucose. As with most endocrine systems it is regulated in a feedback loop manner ensuring a narrow range of glucose levels. As a response to caloric intake insulin is secreted from the pancreas into the bloodstream and absorbed by the insulin sensitive tissues (muscle, adipose tissue and liver). When these tissues have absorbed the needed glucose a signal is sent to the pancreas informing the insulin producing cells that no further insulin is needed, hence inhibiting the insulin excretion. This signaling cascade is know as a negative feedback loop(8).

The major factors in glucose regulation are insulin, glucagon and glucagon-like peptide-1 agonists.

Insulin is produced by the β-cells situated in the endocrine pancreas and secreted as a response to increased plasma glucose levels e.g. after a meal. The secretion of insulin mediates activation of glucose transporters in insulin sensitive tissue as muscle and adipose tissue to increase the uptake of glucose. As response these tissues feed back a negative response to the β-cells mediating a decrease of insulin secretion. Insulin also suppresses the release of glucose from the kidney and liver, which is used as storage for glucose and releases glucose when fasting.

Within minutes of meal digestion the intestinal factors gastrointestinal-inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) is excreted. These factors further augment the level of insulin. GIP only augments the insulin level but GLP-1 also decrease the glucose release from the liver, increase glucose uptake in the muscles, delay gastric emptying, decrease appetite and glucagon secretion as illustrated in figure 1.

Figure 1: GLP-1 agonists effect on different organs



GLP-1 agonists increases the secretion of insulin, insulin synthesis and glucose uptake. Glucose production from the liver and glucagon secretion from the pancreas are decreased. Adapted from Holst & Vilsbøll 2013 (*=animal studies). (6)

The counterpart to insulin is glucagon, a hormone secreted by the pancreatic α-cells. Glucagon predominantly mediates the liver to activate an increase of glucose through breakdown of glycogen. The main activators of glucagon secretion are insulin and glucose, hence hyperglycemia inhibits glucagon secretion and hypoglycemia stimulates it.

In popular terms one could say that insulin and GLP-1 has opposing roles to glucagon. Insulin and GLP-1 promotes energy storage when the nutrition is plenty and glucagon promotes catabolism when nutrition is sparse, thereby making energy accessible. (7)

Type 2 Diabetes

T2DM accounts for 90-95% of all cases of diabetes worldwide and is associated with obesity and cardiovascular risk factors e.g. hypertension, further affecting the morbidity and mortality of this patient group.

Both genetic and environmental factors influence the development of type 2 diabetes. Studies have shown an increased susceptibility of up to 40% for diabetes if a degree relative is diagnosed with diabetes. Environmental factors such as western lifestyle with inactive lifestyle, obesity and highly processed diet interacts with the genetic disposition and increases the risk of developing diabetes.

T2DM diabetes is a progressive developing disease from multiple pathophysiological processes leading to sub-optimal glycemic control. The main pathophysiological processes are insulin resistance, impaired insulin and GLP-1 secretion.(8)

Increased dietary intake of carbohydrates and inactivity affects the insulin sensitivity in the glucose dependent tissues (liver and muscles); hence the uptake of glucose decreases in the glucose dependent tissues and glucose levels increases in the bloodstream. The hepatic insulin resistance results in an overproduction of glucose from the body's glucose storage in the fasting stage, which increase the fasting plasma glucose levels (FPG). As a consequence of the decreased uptake of glucose in the muscles and hepatic overproduction of glucose hyperglycemia after meals develops (postprandial hyperglycemia). Obesity is strongly associated with this insulin resistance(9).

To maintain normoglycemic levels the increased insulin resistance is compensated by an increase of the insulin production by the pancreatic β-cells, if the increased insulin production is sufficient hyperglycemia is prevented. Hyperglycemia is not always dependent on decrease insulin sensitivity since hypoglycemia can occur from abnormal insulin production without decreased insulin sensitivity.

Insulin production and secretion are highly dependent on the amount of functional pancreatic β-cells, loss of β-cells is associated with continuing hyperglycemia, genetic factors and increased levels of free fatty acids. Pre-diabetes is associated with up to 40% β-cell function loss and when diabetes is diagnosed up to 80% can be lost.

Furthermore, impaired incretin effect in type 2 diabetics might increase the disease severity. The incretin effect is the phenomena that oral administration of glucose results in a greater insulin response compared to intravenous or subcutaneous administration, which is suspected to be mediated by the glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both incretins acts on the pancreatic cells but GLP-1 acts on both β-cells and α-cells, which increases the insulin secretion and inhibits the glucagon secretion, respectively. This dual action makes GLP-1 more effective in the blood glucose regulation(10).

The impaired incretin effect is suspected to be a consequence of increased β-cell resistance as studies have shown equal plasma concentrations of GLP-1 in both diabetics and non-diabetics(10).

Complications of type 2 diabetes

Type 2 diabetes patients often present in the clinic before diagnosis as obese with symptoms of hyperglycemia e.g. fatigue and polyuria. Polyuria is caused by the increased excretion of glucose from the kidney into the urine that increases the amount of urine due to the osmotic properties of the glucose in the urine. The increased glucose levels in the urine leads to augmented infections in the urinary tract, which can be treated with simple antibiotics(7).

Some patients may present with macrovascular complications, which is disease of the larger vessels in the cardiovascular system caused by arteriosclerosis and subsequent narrowing of the vessels. Arteriosclerosis is caused by inflammation and damage to the arteries, and together with the increased risk of hypercoagulability in type 2 diabetics the risk of vascular occlusion is higher in diabetics than

non-diabetics. Examples of macrovascular complications are angina, myocardial infarction and stroke(11).
While other patients present with microvascular complications, which is damage of the smaller vessels in the cardiovascular system e.g. the capillaries in the retina of the eye. The pathological mechanisms causing these complications are complex and most mechanisms are being disputed(11). Examples of microvascular complications are retinopathy, nephropathy and neuropathy. When diagnosed with type 2 diabetes patients often have had substantial hyperglycemia for five to ten years prior to diagnosis(7).

Treatment of Type 2 diabetes

The treatment of hyperglycemia is multifactorial and complex due to the heterogeneity of the patients and concomitant pathophysiologic variation together with hyperglycemia e.g. one patient might be severely obese with a significantly heighten blood pressure and an other patient might only be slightly overweight. Hence treatment should be taking account for the individual needs in order to obtain optimal treatment outcomes(7,8,12). Several pharmaceutical treatment options are available in the anti-diabetes cluster, and each has weaknesses and strengths. In the following section the available drugs will be presented together with the European treatment guidelines and the major clinical findings in anti-diabetic treatment from the last decades.

Pharmaceutical landscape of anti-diabetics

The anti-diabetic pharmaceutical landscape can appear as somewhat a jungle with multiple treatment classes and efficacy variance of pharmaceutical in each class. This section will serve as an overview of the different classes of anti-diabetic pharmaceutical treatments and functional characteristics.
Biguanides (metformin) acts on the pancreas in an insulin sparing way, and is very effective in reducing hyperglycemia (HbA1c reduction 1-2%) and has a beneficial effect on the cardiovascular system. Furthermore, metformin reduces the hepatic glucose production(9) and slightly increases the muscular insulin sensitivity(6) while being weight neutral, very well tolerated and displays low risk of hypoglycemia(6)but is associated with gastrointestinal side effects(13).
Sulphonylureas (SU) acts on the pancreatic β-cells and enhances the insulin secretion, which can reduce the HbA1c with 1-2%(13). Sulphonylureas has been shown to reduce the risk of microvascular complications. Adverse effects include a substantial increased risk of hypoglycemia and weight gain(9).
Thiazolidinediones (TZD) enhances the insulin sensitivity resulting in a greater uptake of glucose in the insulin dependent tissues, and can reduce HbA1c 1-2%(13). TZD also reduce the cardiovascular inflammation, which improves the cardiovascular function and decrease the risk of macrovascular complications. Weight gain, fluid retention, edema, fracture risk and congestive heart failure are adverse effects associated with TZD(6). Congestive heart failure is a infrequently adverse effect but should taken into account because of the severity(9).
Sodium glucose co-transporter-2 (SGLT-2) inhibitors acts on the kidney more specifically on the reabsorption of glucose resulting in near normal blood glucose levels caused by increased levels of glucose excreted with the urine. SLGT-2 has been shown to decrease HbA1c levels 0,5-1%, promote weight loss of 2-3.5 kg and decrease blood pressure. The only associated adverse effect is increased risk of urinary tract infections.(13)
Dipeptidyl peptidase-4 (DPP-4) inhibitors act as an inhibitor of the natural occurring dipeptidyl peptidase-4, which is responsible for the degradation and inactivation of GLP-1. As DPP-4 inhibitors essentially prevent inactivation of GLP-1 the benefits and side effects is very similar to GLP-1 agonists(14). Positive effects include HbA1c reduction in the span of 0.7-1.4%, increased insulin secretion, decreased hepatic glucose production and no weight gain(13). Adverse effects associated with DPP-4 inhibitors are gastrointestinal side effects but is less frequent than GLP-1 agonists therapy(14). Furthermore, DPP-4 inhibitors stimulate proliferation and inhibition of apoptosis (cell death) in the insulin producing β-cells, hereby preserving the β-cells mass.
Glucagon-like peptide-1 (GLP-1) agonists mimics the effect of the natural occurring GLP-1, which is a gastrointestinal hormone secreted from the colon in response to ingested food. GLP-1 acts on the

pancreatic α and β-cells mediating increased insulin and decreased glucagon secretion. Furthermore, it has a preservative effect on the critical β-cell mass(14). Depending on the pharmaceutical agent GLP-1 agonists is associated with HbA1c reduction of 1-2% and weight reduction of 1-4 kg(14). Adverse effects associated with GLP-1 agonists therapy is an increased risk of gastrointestinal side effects e.g. nausea.

Table 1: Overview of hyperglycemic pharmaceutical treatment options

Drug Class	Example	Action	Side effects
Biguanides (O)	Metformin	↓ Hepatic glucose production ↑ Muscle insulin sensitivity	
Sulphonylureas (SU) (O)	Glimepiride, glipizide etc.	↑ Insulin secretion	↑ Weight ↑ Hypoglycemia
Thiazolidinedione (TZD) (O)	Pioglitazone	↑ Insulin secretion	↑ Fluid retention ↑ Fracture risk ↑ Heart failure
DPP-4 inhibitor (O)	Alogliptin, sitagliptin	↓ Fasting glucose →Body weight ↑ Insulin secretion ↓ Glucagon secretion ↓ Hepatic glucose production	↑ Gastrointestinal adverse events
SLGT-2 (O)	Canaglifloxin, dapagliflozin	↓ Body weight ↓ Blood pressure	↑ Urinary tract infections
GLP-1 agonist (I)	Exenatide, liraglutide etc.	↓ Postprandial glucose ↓ Fasting glucose ↑ Insulin secretion ↓ Glucagon secretion ↓ Hepatic glucose production ↓ Body weight ↑ Satiety	↑Gastrointestinal adverse events
Basal insulin (I)	Glargine, detemir etc.	↓ Fasting glucose ↓ Hepatic glucose production ↓ Glucagon ↑ Insulin comcentration	↑ Hypoglycemia ↑ Weight
Overview of the most utilized pharmaceutical classes in the treatment of hyperglycemia. O = oral administration I = subcutaneous injection			

Intensive glycemic treatment – is it important?

The effect of intensive treatment and tight glycemic control on cardiovascular events has been investigated in multiple trials in type 1 and 2 diabetes. Most prominent was the United Kingdom Prospective Diabetes Study (UKPDS), Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) and Veterans Affairs Diabetes Trial (VADT).

UKPDS followed newly diagnosed T2DM patients receiving intensive treatment (HbA1c 7%) for 10 years. Compared to the control cohort on conventional treatment the intensive treatment group showed a 25% reduction in microvascular complications. Furthermore, a substantial reduction was shown in cardiovascular disease. These outcomes have been disputed by results from other clinical trials such as ADVANCE and Veterans Affairs Diabetes Trial (VADT), which showed no statistical significant effect on cardiovascular outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial terminated the cardiovascular trial due to increased mortality in patients on very intensive glycemic treatment (HbA1c <6%).

Due to the conflicting results of the various trials, it has been challenging to figure out whether or not intensive treatment and tight glycemic control should be embraced by the treatment recommendations. However subset analysis of ADVANCE, VADT and ACCORD displayed a benefit of intensive treatment in patients with short duration of diabetes and follow-up studies from UKPDS have showed a reduction in myocardial infarction and all cause mortality for patients treated with the intensive regiment.(15). Hence, tight glycemic control is now comprised in treatment recommendation

European Treatment Algorithm Guidelines

The unified treatment recommendations from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) for type 2 diabetes patients highlights that individualized patient treatment and treatment goals are of paramount importance in reaching good glycemic control.

The basic intervention is lifestyle intervention, and when lifestyle intervention is no longer sufficient to reach treatment targets the first line pharmaceutical choice is the low cost metformin, which is generally weight neutral and very low risk of hypoglycemia. Monotherapy with metformin in patients with a high HbA1c (>9%) is rarely sufficient, and it can be reasonable to initiate insulin in these cases.

If HbA1c target is not obtained and maintained within 3 months on metformin monotherapy next option is a two-drug combination of metformin in combination with orally administered sulfonylurea (SU), thiazolidinedione or DPP-4 inhibitors. SU is associated with an increased risk of hypoglycemia and a modest weight gain; thiazolidinedione is associated with weight gain, retention of fluid possibly causing edema; As previously describes are DPP-4 inhibitors associated with a modest weight loss and gastrointestinal side effects. Alternatively subcutaneous injection anti-diabetic agents as GLP-1 agonists or basal insulin can be added in combination with metformin. The GLP-1 agonists are associated with substantial weight loss and low risk of hypoglycemia but also gastrointestinal side effects. Basal insulin is associated with significant decrease in HbA1c but also an increase in hypoglycemia risk and weight gain.

When the patients HbA1c level no longer is within the targeted interval a three-drug combination can be initiated. This treatment regiment consists of more complex and multiple combinations are available. Although adding a non-insulin agent to a two-drug combination has been shown to have some advantages, the addition of insulin does generally show a greater treatment response. The combination of three drugs increases the likelihood of side effects, drug-drug interactions and potentially treatment adherence.(16)

When triple therapy is no longer sufficient to maintain good glycemic control basal insulin is essential. Once daily basal insulin is titrated in concordance with the decreased function of the pancreatic β-cells, hence starting with a low dose with following sequential increments until the patient reaches the targeted glycemic goal on stable dosage. At some point the patient will be unable to remain in control and addition of rapid-acting mealtime insulin (bolus insulin) should be considered to the largest meal of the day, this treatment regiment is called basal-bolus, but clinicians and patients are frequently hesitantly with timely intensification of insulin e.g. from basal insulin only to basal insulin plus mealtime insulin. This hesitance is somewhat due to the fear of hypoglycemia and weight gain that are associated with intensification(17). The natural outcome of the delayed intensification is decreased glycemic control and an increase of associated risk factors. As the disease progresses bolus insulin injections will gradually be needed more frequent; first added to the next largest meal and latter to the third largest meal of the day. As the amount of injections increases so does the treatment complexity since each insulin injection warrants a self-monitoring of blood glucose (SMBG) test in order to administer the right amount of insulin. These factors can potentially result in non-adherence and subsequently poor glycemic control. (16)

As an intermediate step before intensifying the treatment with basal-bolus treatment the addition of a GLP-1 agonist to patients uncontrolled on basal insulin + metformin could have a beneficial impact on the glycemic control and weight compared to proceeding with only basal insulin + metformin. Comparator in the current analysis was basal insulin + placebo based on tendencies from published studies of clinical inertia in clinical practice showing that patients rather start an additional oral anti-

diabetic agent e.g. sulphonylurea rather than intensifying the treatment(18,19). On this basis placebo was chosen as comparator in order to reflect the clinical reality.
Furthermore, the need for basal-bolus treatment could potentially be postponed.(16)

OBJECTIVE

Type 2 diabetes patients insufficient controlled on basal insulin + metformin is often hesitant with intensifying the insulin treatment to basal-bolus due to the increased risk of hypoglycemic events and weight gain. Subsequently this patient group remains in poor glycemic control, with increased risk of microvascular and macrovascular complications as a consequence, until they initiate basal-bolus treatment. The addition of GLP-1 agonists to the basal insulin treatment regimen has been shown to have a beneficial effect on glycemic control and weight.
Thus, a cost-effectiveness analysis was conducted in order to investigate the cost-effectiveness of adding a GLP-1 analog to existing basal insulin treatment compared to addition of placebo in a type 2 diabetes population insufficient controlled on basal insulin + metformin from a societal perspective over a timeframe of 50 years.

GLP-1 ANALOGUES IN THE TREATMENT OF DIABETES

Due to the anti-diabetic and weight reductions of GLP-1 agonist they have been established as an effective add-on treatment to metformin and in lesser extent in combination with basal insulin(20). The available options for GLP-1 agonists have different injection frequencies, molecular composition and treatment outcomes. The present available GLP-1 agonists (table 2) are exenatide (Bristol-Myers Squibb), liraglutide (Novo Nordisk) and lixisenatide (Sanofi-Aventis), but several compounds are in late clinical phases.
The active component of exenatide is artificial produced exedin-4 derived from the venom of the gila monster lizard and are available in two formularies; one being injected twice daily and the other once weekly. Exenatide has been shown to reduce HbA1c with 0.8-1.0% and weight with 1.5-3.0 kg after 30 weeks of treatment in patients uncontrolled on metformin monotherapy. Lixisenatide is like exenatide based on exedin-4 and are injected once daily. Lixisenatide has been shown to reduce HbA1c with 0.87% and weight with 1 kg after 24 weeks of treatment in patients uncontrolled on metformin(21). Liraglutide is a human GLP-1 analog administered once daily. Liraglutide has been shown to reduce HbA1c with 1.0% and weight with 2.6 kg after 26 weeks of treatment in patients uncontrolled on metformin(22).

Table 2: Overview of current GLP-1 analogs approved for combination with insulin

Name (Brand name, manufacturer)	**Combination with insulin**	**EMA approval date**
Exenatide (Byetta®, Bristol-Myers Squibb)	Yes, with insulin glargine ± metformin	16-02-2012
Lixisenatide (Lyxumia®, Sanofi-Aventis)	Yes, with basal insulin ± metformin	01-02-2013
Liraglutide (Victoza®, Novo Nordisk)	Received positive opinion for combination with basal insulin ± metformin	Received positive opinion from EMA 20-03-2014(23)
Overview GLP-1 agonists currently available for Danish diabetes patients, their status on combination with insulin together with label indications and approval date of this indication by the European Medicines Agency.		

Real-world data for the use of GLP-1 analogs in combination with basal insulin in Denmark was investigated by *Pottegård et al*. 2014(24) through a retrospective analysis of the Danish National

Prescription Registry (DNPR) for utilization of liraglutide QD and exenatide BID. The study found 17866 and 2032 patients using liraglutide and exenatide regularly. Of these patients 6877 (38.5%) and 878 (43.2%) of liraglutide and exenatide used insulin concomitantly with GLP-1 analogs. The average age and duration of diabetes for the whole population, not just the sub-population with concomitantly, using liraglutide and exenatide was 60 and 54 years with duration of diabetes of 6.3 and 6.4. The sub-population using concomitant insulin with GLP-1 analogs is suspected to have longer duration of diabetes due to the more severe disease progression. Glycemic control of the cohorts was 8.3% and 8.5% for liraglutide and exenatide respectively.
These findings show that the combination of GLP-1 agonists and basal insulin are being used both in line with the label (exenatide) and off-label (liraglutide). Hence, an unmet need is present for the Danish type 2 diabetes population.

Trial Overview of Insulin and GLP-1 agonist combination

PubMed and Google Scholar were utilized as of February 2014 to identify articles publishing results from clinical trials investigating the combination of insulin and glucagon-like peptide-1 agonists in type 2 diabetes mellitus patients. The search protocol included GLP-1 agonists with insulin combination indicated in the label approved by the European Medicines Agency. These consist of Byetta® (exenatide) manufactured by Bristol-Myers Squibb and Lyxumia® (lixisenatide) manufactured by Sanofi-Aventis. Furthermore, clinicaltrials.gov and PubMed were queried to identify trials for GLP-1 agonist agents not yet approved for combination with insulin e.g. Victoza® (liraglutide) manufactured by Novo Nordisk.
The full search enquired in PubMed and Google Scholar was:
("glp 1" OR "glucagon like peptide" OR "glucagon like peptide 1" OR "liraglutide" OR "exenatide" OR "lixisenatide") AND ("basal insulin" OR "long acting insulin" OR "detemir" OR "glargine" OR "degludec") AND ("basal bolus" OR "basal bolus insulin" OR "aspart" OR "lispro" OR "glulisine").
The only exclusion criterion was type 1 diabetes mellitus.
The initial search identified 2489 articles. Articles not meeting the following parameters were excluded: English language, human species, and clinical trial. Resulting in 298 articles eligible for further assessment. The identified articles were scanned for concomitant DPP-4 administration, length of study <24 weeks, retrospective study protocol and non-placebo controlled, and excluded if any of these were present. Four articles meet all search criteria: *Buse et al*. 2011(18), *Seino et al*. 2012 (GetGoal-L-Asia)(25), *Riddle et al.* 2013 (GetGoal-L)(12) and *Riddle et al*. 2013 (GetGoal-Duo)(26). *Riddle et al* 2013 (GetGoal-Duo)(26) was excluded due to initiation of both insulin and GLP-1 within 12 weeks, this approach is unlikely to represent the clinical reality since most patients is first initiate on insulin or a GLP-1 agonist and then intensified with addition of insulin or a GLP-1 agonist when glycemic control is no longer sufficient. *Seino et al*. 2012 (GetGoal-Asia)(25) was excluded due to specific racial characteristics of the study population being unrepresentative for the specific country of analysis.
Publication bias, the phenomenon that positive literature is more likely to be published than studies showing low or negative efficacy can be an issue when searching for literature. This only impacts the relevancy of the analysis if the studies not published studies differ from the identified studies. No indication of publication bias were observed in the systematic literature search but cannot definitely be ruled out.

Overview of Trials Adding GLP-1 to insulin

Buse et al 2011(18): In 2011 *Buse and colleagues* published the results of the first double blinded and placebo controlled study of exenatide twice daily (BID) added to existing basal insulin treatment with insulin glargine. Adults treated with existing insulin glargine alone or combined with metformin and/or

pioglitazone (TZD) were randomized to placebo (n= 123) or exenatide BID (n=138). Insulin dosage was titrated on a basis of a treat-to-target algorithm with a fasting blood glucose level below 5.6 mmol/L. The mean duration of diabetes of both treatment cohorts was 12 years. Both cohorts were treated in 30 weeks, with subsequent results: the exenatide BID cohort showed a larger decrease in HbA1c compared to the placebo cohort respectively -1.74 (-1.91 to -1.56 [95% CI]) and -1.04 (-1.22 to -0.86 [95% CI]). Furthermore, the exenatide cohort exhibited a decrease in weight compared to a weight gain in the placebo cohort respectively -1.78 kg (-2.48 to -1.08 [95% CI]) and +0.96 (0.23 to 1.70 [95% CI]). The difference between the cohorts was similar irrespective of metformin, pioglitazone, age, sex and gender.

The increase in insulin dosage was significantly lower in the exenatide BID cohort compared to the placebo cohort 13 units/day and 20 units/day respectively. The greater glycemic control was observed without increased risk of hypoglycemia; hence the number of hypoglycemic events per patient year did not significantly differ between the exenatide and placebo cohorts. The proportion of minor hypoglycemia registered was similar between cohorts. In the placebo cohort one patient experienced two major hypoglycemic events, both nocturnal.

Adverse events caused 13 patients on basal insulin + exenatide and 1 patient on basal insulin + placebo discontinued the study. The adverse events were predominantly gastrointestinal events: nausea, diarrhea, vomiting, headache and constipation. In the exenatide group 41% experienced nausea compared to 8% in the placebo group, 18% of the exenatide group experienced diarrhea compared to 8% in the placebo group, vomiting were experienced by 18% of exenatide cohort and 4% of placebo cohort, headache were experienced by 14% of exenatide recipients and 4% of placebo recipients and 10% of the exenatide group experienced constipation compared to only 2% in the placebo group.(18)

Riddle et al. 2013 (GetGoal-L)(12): A 24-week randomized placebo-controlled trial adding once-daily (QD) lixisenatide to existing basal insulin treated type 2 diabetes patients with inadequate glycemic control despite insulin treatment and oral anti-diabetic medicine (metformin). The 495 participating patients were randomized to either add lixisenatide or placebo onto their existing basal insulin treatment, which was left unchanged in the majority of patients. The mean duration of diabetes was 12.5 years, mean duration of insulin treatment 3.1 years with mean insulin dosage 55 units/day and a baseline HbA1c of 8,4%. The average ages for both groups were 57 years. Previous to the trial patients had been treated with various insulin formulations, some with basal long-acting insulin analogs as insulin glargine and insulin, intermediate acting NPH insulin and some was treated with a combination formula of basal insulin and bolus insulin called Premix.

Mean change in HbA1c at 24 weeks decreased by -0.7 ± 0.1% in the lixisenatide cohort compared to the decrease in the placebo cohort by -0.4 ± 0.1%. The percentage of patients reaching the goal of a HbA1c level <7% was higher in the lixisenatide cohort compared with the placebo cohort, 28% and 12% respectively. No statistical difference of FPG was observed. A loss of body weight of -1.8 kg (SE ± 0.2) was observed in the lixisenatide cohort compared to -0.5 kg (SE ±0.3) in the placebo cohort. Basal insulin dosage decreased in both cohorts but more substantial in the lixisenatide cohort -5.6 units/day (SE ±1.3) compared to the placebo cohort -1.9 units/day (SE ±1.6). Symptomatic hypoglycemia of <3.3 mmol/L was reported in 26.5% of patients in the lixisenatide cohort and 21.0% in the placebo cohort. The majority of hypoglycemic events were nocturnal and happened in the first weeks of treatment. Four patients in the lixisenatide cohort experienced a severe hypoglycemic event of which two was caused by missed meals.

73.5% of lixisenatide recipients experienced at least one adverse event compared to only 68.3% of placebo recipients. Discontinuation rate due to adverse events was 7.6% and 4.8% in lixisenatide and placebo groups. Most common adverse events were nausea and vomiting.

Since the enrolled patients were in poor glycemic control despite of being treated with basal insulin and metformin improvement in glycemic control in this population was expected to be difficult according the study investigators. (12)

Outcome differences of the clinical trials

The outcomes of the two trials differ in several aspects. *Buse et al.* 2011(18) showed a greater reduction of HbA1c compared to *Riddle et al.* 2013(12) in both basal insulin + GLP-1 agonist group and basal insulin + placebo group. The reduction in the placebo cohort are suspected to be due the clinical trial setting, which improve patient attention to glycemic control and closer monitoring from healthcare professionals. A greater percentage of patients treated with basal insulin + GLP-1 agonists in Buse et al 2011 reached the targeted glycemic level (60%) compared to *Riddle et al*. 2013(12) (28%).

Both the GLP-1 agonist and placebo cohort in *Riddle et al*. 2013(12) showed a weight loss. In *Buse et al.* 2011(18) weight loss was only associated with GLP-1 agonist treatment, whereas placebo was associated with weight gain.

The hypoglycemic event rates did also differ since the rate of non-severe hypoglycemic events for the placebo group in *Buse et al.* 2011(18) was lower compared to the GLP-1 agonist group, whereas the tendency was opposite in *Riddle et al*. 2013(12). The rate of severe hypoglycemic events likewise differed since only the placebo group in *Buse et al.* 2011(18) experienced severe hypoglycemic events and in *Riddle et al.* 2013(12) only the GLP-1 agonist group experience severe hypoglycemic events.

Extracting and pooling data from RCT publications

Combination of data from multiple trials can be advantageous in order to compare the efficacy of several interventions. But some pitfalls exist when such combination is performed such as using simple summation of the trial or study results if such approach is used the data are treated as if originating from one trial, and can potentially result in misleading outcomes. Thus a calculated weighted average is utilized to avoid such issues. Before calculating a pooled mean value investigations of whether it makes clinical sense of combining the results. The studies at hand show similarities in respect to baseline population e.g. duration of diabetes, age and baseline glycemic control (HbA1c). Furthermore, both studies reports the same effect measures e.g. HbA1c, weight reduction and hypoglycemic events. Differences between the studies as the time frame of the study, the number of participating patients in each trial arm background treatment of the population such as previous insulin treatment and affect the choice of statistic method used to estimate the combined mean and variance. The random effects model was applied for the estimation due to the variation of study length, participating patients, background treatment such as different basal insulin and +/- TZD and difference in GLP-1 analog compounds.

Table 3: Overview of treatment outcomes from *Buse et al.* 2011(18) and *Riddle et al.* 2013 (12)

	***Buse et al.* 2011(18)**				***Riddle et al.* 2013(12)**			
Outcome	**Placebo**	SD	**Exenatide**	SD	**Placebo**	SD	**Lixisenatide**	SD
Baseline HbA1c	8.53	0.96	8.35	0.85	8.40	0.84	8.40	0.84
HbA1c reduction	1.04	0.30	1.74	0.29	0.40	0.10	0.70	0.10
% reaching HbA1c <7%	35.00	-	60.00	-	12.00	-	28.00	-
HbA1c post treatment	7.49	0.3	6.61	0.3	8.10	1.2	7.80	1.2
Weight reduction	0.96	0.61	-1.78	0.60	-0.50	0.55	-1.80	0.45
Duration of diabetes	12	7	12	7	12.4	6.3	12.5	7

Age	59	10	59	9	57	10	57	10
Non-severe hypoglycemic event rate per 100 patient year	120.00	-	140.00	-	363.41	-	313.77	-
Severe hypoglycemic event rate per 100 patient year	2.46	-	0.00	-	0.00	-	4.88	-

Mean values (table 3) for the two placebo and the two intervention arms were combined to form a combined mean estimate for the combined placebo and GLP-1 agonist arms. To adjust for the difference in each arm the outcomes was weighted by the inverse variance within the study and the variance between the two studies(27). Results from *Buse et al.* 2011(18) was published as confidence intervals which was used to obtain the standard deviation by applying the following equation and subsequently squared to obtain the SD: SE= (upper limit - lower limit)/3.92.
No variances of hypoglycemic event rates were reported in either study, hence a weighted mean were not possible to be calculated and a simple combined mean were utilized as a estimate.

Table 4: Overview of combined mean values and standard deviation

	Combined values			
Outcome	**Placebo**	SD	**GLP-1**	SD
Baseline HbA1c	8.46	0.45	8.38	0.42
HbA1c reduction	0.56	0.08	1.13	0.26
% reaching HbA1c <7%	23%	-	38%	-
HbA1c post treatment	7.61	0.24	6.99	0.55
Weight reduction	0.21	0.53	-1.79	0.26
Duration of diabetes	12.21	3.32	12.25	3.50
Age	58.00	5.00	58.04	5.64
Non-severe hypoglycemic event rate per 100 patient year	231.97	-	297.59	-
Severe hypoglycemic event rate per 100 patient year	1.04	-	3.44	-
The combined outcomes of the two placebo and two intervention arms using the random effects model.				

Furthermore, the BMI change from baseline to end of treatment was calculated on the basis of the weight change in each group applied in the equation for BMI= weight/ height^2. The average height of each cohort was isolated in the equation and derived by inserting the published weight for each respective cohort. Assuming that the average height remains constant from baseline to end off trial the BMI change could be calculated. Subsequent the average BMI change was combined in similar way as the remaining combined outcomes resulting in a combined BMI change of -0.65 and 0.04 for GLP-1 and placebo respectively.

HEALTH ECONOMICS

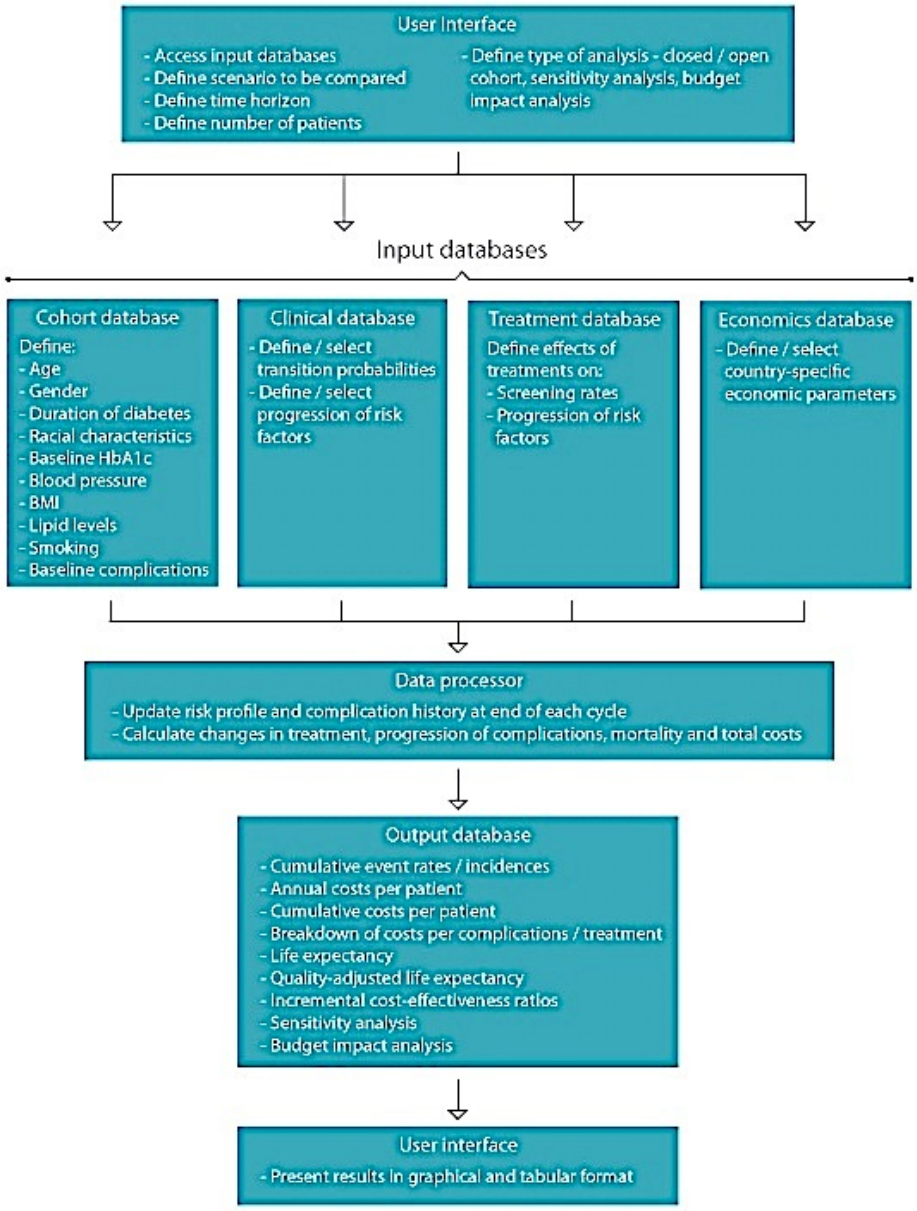
Health economic modeling is applied to estimate the impact of health care interventions in terms of the clinical and cost outcomes in a specific time horizon. Contrary to clinical and observational trials health economic modeling allows estimation of the costs and health-related quality-of-life over the complete patient lifetime. Generally in the study of diabetes most studies is of relative short duration but a few long-term trials has been conducted such as the Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS)(28) with respective run-times of seven and twelve years, but these studies do not provide an estimation of the costs and quality-of-life related to diabetic complications.

The complications of diabetes have a major influence on the patient's life and functioning but also on the costs of healthcare providers. As previous described the UKPDS study showed that morbidity, mortality and complications could be reduced by tight glycemic control. Hence, new healthcare interventions that enhance the glycemic control are likely to also reduce the risk of diabetic complications and the associated costs.

Description of the CORE diabetes model

The IMS CORE Diabetes model is a diabetes specific model licensed under the consultancy corporation IMS Health Inc., which is accessible for medical corporations against a payment. When the model is used in the reimbursement process authorities can be granted access to the model in order to enhance the transparency of the model input, calculations and results. The CORE Diabetes model is a multi-layered Internet application interconnected to a central server database performing mathematical model calculations. Four elements make up the basis of the model: the user interface, the input databases, the data processor and the output databases (figure 2). The user interface lets the user define the structural design of the model by defining scenarios to be compared, time horizon, number of patients and type of analysis. Factors related to the cohort, clinical, treatment and economics are entered in separate databases and processed by the data processor, which calculate the costs, QALYs, event rates and incremental cost-effectiveness. These results are stored in the outcomes database, and presented as cumulative cost, annual cost, incremental cost-effectiveness ratio, life expectancy, quality-adjusted life expectancy and survival curves. Input databases and data processor will be described more in depth in the following sections.

Figure 2: Overview of the IMS Core diabetes model



Overview of components comprising the IMS CORE diabetes model. http://www.core-diabetes.com/about-the-cdm.html

Input databases

The input databases are the base for the simulation calculations, and are comprised of a cohort database, a clinical database, a treatment database and an economics database.

Cohort database

All properties of the cohort is described in this database including patient demographics (age, gender, ethnic group and duration of diabetes), baseline risk factors (HbA1c levels, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, body-mass index, number of cigarettes smoked per day and alcohol consumption) and baseline complications (myocardial infarction, angina, peripheral vascular disease, stroke, congestive heart

failure, atrial fibrillation, left ventricular hypertrophy, microalbuminuria, gross proteinuria, end-stage renal disease, retinopathy, severe vision loss, macular edema, cataract, uninfected/infected foot ulcer, gangrene, healed ulcer, amputation history and neuropathy complications. These cohort properties define each generated patient of the simulation. The probability of developing a complication, progressing to a more advanced state of the disease or dying is compared to a random number generated from a uniform distribution, between 0 and 1, for any given event. Is the drawn number less than or equal to the probability for the event then the event is considered to have occurred.
The cohort baseline characteristics are defined at the start of the simulation while risk factors and complications history are updated at the completion of each simulation cycle, thereby accounting for the changing complication risk and pathophysiological progression of the disease.(29)

Clinical Database

Medical and epidemiological data, derived from published literature, is entered in the model in order to calculate the clinical outcomes. These data consists of a group of probabilities and risk factors for occurrence of acute events and disease progression based on patient states, characteristics and physiological parameters. Further elaboration will follow in the data processing section.(29)

Treatment Database

Data related to the treatments and their attributes are entered in this database. The data consists of a treatment pathway, treatment effect and subsequent impact on each physiological parameter in the simulation.
Due to the progressive nature of diabetes both treatment groups will eventually be forced to an intensification of treatment resulting in a treatment switch to basal insulin + bolus insulin (BB). The treatment switch are assumed to be a full basal-bolus regiment, hence patients receive one injection of basal insulin and three mealtime (bolus) injections each day. This might not reflect the real-world clinical practice since the majority of patients will intensify the insulin treatment in sliding scale manner e.g. starting with one injection of bolus insulin progressing to three daily bolus injections eventually.
Treatment switch were conditional of the duration of years on the specific treatment. In the present analysis it is assumed that patients treated with both GLP-1 agonists and placebo remains on the respective treatments for five years and consequently experience treatment failure within the fifth treatment year. This assumption is based on retrospective results published by *Khunti and colleagues*(19), which investigated the clinical inertia in 80000 diabetic patients. They found that patients treated with oral anti-diabetics stayed on the treatment regiment for >5 years before initiating insulin treatment. Due to the lack of published literature on clinical inertia from basal insulin + GLP-1 to basal bolus insulin, it is assumed that the tendency is similar as with oral anti-diabetics to basal insulin(19).

Economics Database

The data included in the economics database are comprised by direct and indirect costs, discount rates and quality-of-life data. Direct costs consist of costs of patient treatment, medication, consultations and acute events and long-term complications.(29)
Indirect costs used in the analysis consist of the absenteeism or days off work (DoW) and the subsequent loss of productivity expressed in lost salary associated with diabetic complications as hypoglycemia, myocardial infarction and foot ulcer. A Danish registry analysis of 34882 diabetes patients days of work after diabetes related complications published in 2013 was utilized as representative estimates for the days of work for the population in the analysis at hand(30). The absenteeism or days off work associated with severe hypoglycemia events was derived from a French study, which found that a severe hypoglycemic event was associated with a hospital stay of 6.6 days. See supplement 1 for full description of indirect costs.
Retirement age was assumed 65 years and first year of income was assumed to be at 20 years. Mean salary was derived from Statistics Denmark (ww.dst.dk) using the mean national salary of 286645

DKK from 2013 for both male and females. The number of workdays per year of 235 days was calculated on the basis of a full year with 5 weeks vacation and weekends subtracted. The human capital approach was used in the calculation of indirect costs.

Costs of patient treatment include the use of utensils such as self-monitoring blood glucose test, needles and lancets, and prices are derived from www.teststrimler.dk using the cheapest option available. Medication costs associated with treatment such as insulin, GLP-1 agonists, statins, metformin, ACE inhibitors etc. are derived from the database www.medicinpriser.dk governed by the Danish Health and Medicines Authority, hereby insuring that most recent prices are applied (table 4).

Table 4: Price overview of medication and utensils

Pharmaceutical	**Pack price**	**Units**	**Price per unit**	**Cost per daily dose**
Basal insulin				
Lantus (insulin glargine)	428.96	1500	0.28	0.29
Metformin				
Metformin Aurobindo 500 mg	25.84	100	0.25	0.26
Bolus insulin				
Actrapid penfill	279.40	1500	0.18	0.19
Insuman rapid solostar	172.00	1500	0.11	0.12
Mean				0.15
GLP-1				
Byetta (Exenatide 10 microgram) (BID)	839.52	60	13.99	27.98
Lixisenatide 20 microgram (QD)	762.32	28	27.23	27.23
Liraglutide 6mg/ml (QD)	840.28	30	28.00	28.01
Mean daily cost of all GLP-1s				27,74
Utensils				
SMBG Bayer Contour Next	152.64	25	6.11	6.11
Needles Penfine	101.76	100	1.02	2,04
Lancets BD Fine+	101.76	200	0.51	1.02
Total				9.16

Overview of the pack price, pack units, price per unit and cost per daily dose of medication and utensils.
Prices are derived from www.medicinpriser.dk and www.teststrimler.dk.
All prices are in DKK

When available generic pharmaceuticals were used in the calculation of the total medication costs. Treatment guidelines were obtained from the Danish Health and Medicine Authority or published literature when available or from www.pro.medicin.dk. All prices are excluding VAT as this is considered a transfer cost.
Treatment with basal insulin and GLP-1/placebo is assumed to require one injection of basal insulin, three metformin pills, one injection of GLP-1 agonist/placebo and the use of two sets of utensils (SMBG test strips, needles and lancets). The daily mean basal insulin is based on the mean combined

values extracted from the trials published by *Buse et al*. 2011(18) and *Riddle et al*. 2013(12); 48.5 units/day for the placebo treated cohort and 41.5 units/day for the GLP-1 agonists treated cohort. The daily dose of basal insulin is assumed to be equal in both groups after treatment failure and subsequent treatment switch to basal-bolus, due to the substantial effect of bolus insulin on glycemic levels. Thus, basal insulin was assumed to be 48.5 units/day in both groups after switching to basal-bolus treatment. Bolus insulin was assumed injected three times a day. The cost of placebo is assumed zero.
The annual medicines costs for the various cohorts are depicted in table 5.

Table 5: Calculation of the annual cost for basal insulin + placebo and for subsequent basal-bolus after treatment failure and switch

Basal insulin + placebo	**Unit cost**	**Daily dose**	**Daily cost**	**Annual cost**
Basal insulin	0.29	48.5	13.87	5065.9
Utensils	9.16	2.0	18.32	6690.2
Metformin	0.26	3.0	0.78	283.1
Total				**12039.3**
Basal insulin + GLP-1 agonists				
Basal insulin	0.29	41.5	11.87	4334.7
GLP-1 agonists	36.81	1.0	36.81	10131,9
Utensils	9.16	2.0	18.32	6690.2
Metformin	0.26	3.0	0.78	283.1
Total				**17105,3**
Basal bolus post placebo				
Basal insulin	0.29	48.5	13.87	5065.9
Bolus insulin	0.15	3.0	0.45	164.9
Utensils	9.16	2.0	18.32	6690.2
Metformin	0.26	3.0	0.78	283.1
Total				**12204.1**
Basal bolus post GLP-1				
Basal insulin	0.29	48.5	13.87	5065.9
Bolus insulin	0.15	3.0	0.45	164.9
Utensils	9.16	2.0	18.32	6690.2
Metformin	0.26	3.0	0.78	283.1
Total				**12204.1**

Calculation of the annual cost for basal insulin + placebo and for subsequent basal-bolus after treatment failure and switch. Similar calculation can be found for the basal insulin + GLP-1 agonists and subsequent basal-bolus after treatment failure. All price in DKK.

The costs associated with acute events and long-term complications were derived from the Danish DRG-database for 2014 when possible, if a fitting DRG-tariff was not available estimates from published literature was identified through systematic literature search. First choice was literature with

estimates from Denmark or Scandinavia due to resemblance in health care systems and population demographics. The full overview can be found in supplement 2.

Discount rates are separated in the CORE model for clinical and cost outcomes, hereby enabling differential discount rates but in the present analysis equal rates of 3.5% were used for both clinical and cost outcomes in accordance with ISPOR guidelines(31).

Quality-of-life data are comprised by utilities or disutilities associated with acute events and patient disease states. The utilities and disutilities applied in the current analysis is predominantly derived from the UKPDS 62 study(32) in which 3192 diabetes patients in the UKPDS study responded to an EQ-5D questionnaire. The researchers applied an tobit regression in the analysis of the measured tariff in order to eliminate the issue of scoring above 1 (perfect health) in the EQ-5D instrument(32).
Health-related quality-of-life (HRQoL) estimates for neuropathy and severe vision loss are derived from a British study of utility values associated with diabetic retinopathy. Several instruments were used to estimate the utilities in a population of diabetics, diabetics without diagnosis and the general public: EQ-5D, Health States Utility Index (HUI-3) and National Eye Institute Visual Functioning Questionnaire-25, thereby comparing generic measurements with standard gamble(33). Retinopathy estimates are derived from *Sharma and colleagues*(34) using time-trade off (TTO) to investigate the utilities associated with diabetic retinopathy(34). Renal transplant and peripheral vascular disease HRQoL estimates are derived from *Tengs and Wallace*(35).
HRQoL estimates for hypoglycemic events are derived from a study analyzing the pooled data from two questionnaires; the Hypoglycemia Fear Survey (eight questions worry sub-scale) and EQ-5D(36). A full overview of applied utilities can found in supplement 3.
Quality-of-life years adjustment for BMI derived from a multiple regression approach factoring in TTO scores derived from the CODE-2 study(37) were applied. Each BMI unit above 25 kg/m^2 is associated with a disutility of 0.0038.

Data Processing

The data stored in the input databases comprise the calculation basis for each simulation performed by a remotely located data processor programmed in C++ (Microsoft® Visual Studio 6,0). To capture the long-term complications and the progressive nature of diabetes the CORE Diabetes Model use a combination of Markov modeling and Monte Carlo simulation using tracker variables.
Markov models are comprised by a series of states from which transition to one or multiple other states can occur e.g. healthy, ill or dead. Transition between states in the model is dependent on transition probability. Hence, for each model cycle there is a probability that the subject will remain in the current state or transition to a different state e.g. from healthy to ill. For some states transition is impossible, such as death.(29)
Each state is associated with a cost and utility value; from these can an expected value of the effects and costs be calculated by weighting the time spent in the given state. When running over several cycles the Markov model enables an assessment of the long-term outcomes such as life expectancy, QALY and costs for an entire patient population.
The cycle length of a Markov model can be days, months or years. The present analysis utilizes a cycle length of a year except for foot ulcer (one month) and hypoglycemia (three months). The time horizon was set to 30 years, resembling a full lifetime of the majority of type 2 diabetics from treatment initiation when taking the mean age of the patients.(29)
Markov modeling requires that each disease state is individually defined and that the states are mutually exclusive which might not be representative of the real world. Since it is well known that patients can develop complications in multiple organ systems simultaneous, one complication can increase the likelihood of developing a complication in another system. In the IMS CORE model tracker variables have been implemented to overcome the memory-less markovian properties, allowing interaction between the complication sub-models whilst running a second order Monte Carlo simulation. All sub-models run concurrent in parallel hence enabling the patients to develop several

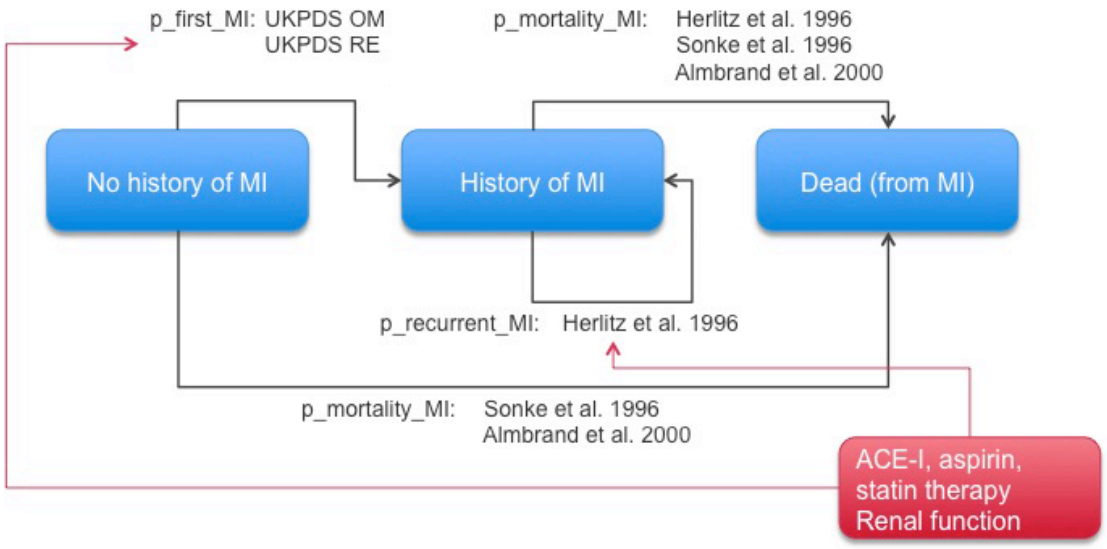
complications within the same cycle and ultimately over the total run-time. Furthermore, developing a complication can potentially influence the transition probability in other relevant sub-models e.g. developing neuropathy increases the risk developing a diabetes related foot ulcer.(29)

In the CORE Diabetes model both first and second order Monte Carlo simulations with distributions can be applied on transitions probabilities.
Monte Carlo simulation is a stochastic simulation utilized to assess the variability and uncertainty surrounding the input parameters of the model. The expected values are calculated multiple times and in each simulation a random draw process between 0 and 1 is performed on each of the parameter distributions applied on the model. Is the drawn value equal or above the probability the event is considered to have happened. The result is a large number of expected effects and costs reflecting the parameter uncertainty of the model. First order is mostly used to assess the variability of the model, whereas second order, also called probabilistic sensitivity analysis, is applied to assess the uncertainty in the parameters of the model.

Sub-models

The CORE model uses 15 Markov sub-models to simulate each of the following different diabetes associated complications: myocardial infarction, angina, congestive heart failure, peripheral vascular disease, neuropathy, foot ulcer, retinopathy, macular edema, cataract, nephropathy, hypoglycemia, lactic acidosis, stroke and non-specific mortality.
To simulate the patient progress through the different Markov states each sub-model utilizes probabilities of time, state and time in state.(29)
Apart from the complications sub-models one additional sub-model exists in the model related to the treatment sequence, which simulates the alternations in treatment pathway caused by treatment failure in controlling the hyperglycemia.(29)

Figure 3: Myocardial infarction sub-model



Myocardial infarction sub-model as an example of a sub-model used in the CORE diabetes model. Different states are associated with distinct probabilities which are influenced by factors e.g. medication.

The **Myocardial infarction (MI)** sub-model is comprised by three distinct states: No history of MI, History of MI and Death following MI. Probabilities for state transition is based on the UKPDS risk engine, this risk model is diabetes specific and factors in HbA1c, systolic blood pressure, cholesterol levels, age, sex, smoking, race and time since diabetes diagnosis in the probability calculation of first MI occurrence derived from the UKPDS 65 study(38). Risk of recurrent MI is based on Swedish data and is dependent on the years after the initial MI(39).
Like the probability of recurrent MI is the probability of death following a MI event dependent on time after the MI event. Sudden death probability after MI is 0,393 for men and 0,364 for women(40). Furthermore, probabilities of death within a year of MI are indexed by age independently for gender and first MI and recurrent based on data from *Almbrand and colleagues*(41). Various risk adjustments are applied to the MI sub-model to factor in glycemic control, renal function and aspirin, statin and ACE inhibitor treatment (Supplement table 4).(29)

The **Angina** sub-model is comprised by two states: No angina and History of angina. Probability calculation of developing angina is based on a regression model developed by *D'Agostino and colleagues*(42) using data from the Framingham study(42), which predicts the probability of developing any coronary heart disease, angina and coronary death. The proportion of patients with angina is then multiplied with the predicted probability in order to compute the probability of developing angina. Proportion of patients developing angina is likewise derived from the *D'Agostino*(42) publication, and are 0,42 for men and 0,621 for women(42).

The **Congestive heart failure (CHF)** is comprised by three states: No congestive heart failure, History of congestive heart failure and Death following congestive heart failure. Again a logistic regression model from the Framingham study was used, which factors in left ventricular hypertrophy, heart rate, systolic blood pressure, age, valve disease, congestive heart disease and diabetes(43). (29)
Probabilities for death following a CHF event is derived from a survival analysis publication by Ho et al. of the subjects in the Framingham study(44), and is indexed by gender and age.
Risk adjustment for a CHF event are adjusted with a 16% for each reduction of 1% in HbA1c levels, which is based on the UKPDS 35 study (45)(supplement 5).

The **Peripheral vascular disease (PVD)** sub-model is comprised by two states: No PVD and PVD. A logistic regression based on the Framingham study that factor in the associated risk of blood pressure, hypertension, diabetes, smoking, gender, age, cholesterol and concomitant heart disease was used to calculate the state transition probabilities(46).(29)
These probabilities are adjusted for HbA1c levels based on data from the UKPDS 35 study(45).

The **Neuropathy** sub-model is comprised by two states: No neuropathy and neuropathy.
Prevalence and transition probabilities of neuropathy are based a publication by *Partanen and colleagues* in 1995(47). The prevalence is depended by duration of diabetes. Risk adjustments for HbA1c and systolic blood pressure changes are based on the UKPDS 34 study (48)(supplement 6).

The **Stroke** sub-model is comprised by three distinct states: No history of stroke, history of stroke and death following stroke. The risk of first stroke is calculated on the basis of the UKPDS risk engine, which is diabetes specific and factors in age, duration of diabetes, systolic blood pressure, smoking, cholesterol ratio and atrial fibrillation(49).(29)
Recurrent stroke, death within 30 days following stroke and death due to long-term complications after a stroke probabilities are derived from a Swedish 14 year follow-up study of survival and recurrent strokes in a 334 cohort(50). All probabilities are distinct for each gender and indexed by age.
First stroke probability risk adjustments are adjusted by the use of medication. Thus, aspirin, ACE inhibitors and statins reduces the probability with 14%, 19% and 33% respectively (6,11,51-53). Recurrent stroke probability risk adjustments are likewise dependent on aspirin and ACE inhibitor use with relative risk reduction of 22%, 16% and 28% respectively.

The **Foot ulcer and amputation** sub-model is comprised by nine states: No foot ulcer, uninfected foot ulcer, infected foot ulcer, healed foot ulcer, uninfected recurrent foot ulcer, infected recurrent foot ulcer, gangrene, history of amputation and death.(29)
Transition probabilities are derived from Swedish cost-effectiveness data published by *Persson* et al.(54), in which markov model transitions were used. All transition probabilities can found in supplement 7.
Foot ulcer development is linked to PVD and neuropathy, and is indexed by patients being in low, moderate or high risk. Patients in low risk show no previous PVD or neuropathy, moderate risk patients have a history of either PVD or neuropathy and high risk patients have a history of both PVD and neuropathy(55).(29)

The **Retinopathy** sub-model is comprised by states of disease status: No retinopathy, background diabetic retinopathy (BDR), proliferative diabetic retinopathy (PDR) and severe vision loss (SVL).(29)
Probabilities of state transitions are derived from an Australian visual impairment study investigating the five year incidence of diabetic retinopathy in a total of 121 diabetes patients(56). Probabilities of progressing from PDR to SVL with and without laser surgery was derived from a xenon arc photocoagulation laser treatment study in diabetic retinopathy patients(57).
Risk adjustments for HbA1c level, systolic blood pressure was derived from the UKPDS study(58) and the WESDR study (18,59) (supplement 8). ACE inhibitors have been shown to have an impact on the progression to BDR and PDR in the EURODIAB study(60); hence a risk adjustment of 25% and 81% is applied for patients treated with ACE inhibitors. American epidemiologic data was utilized racial risk adjustments derived from multi-ethnic studies of diabetic retinopathy patients(12,61).(29)

The **Macular edema** sub-model is comprised by three states: No macular edema (ME), macular edema and severe vision loss. Transition probability for ME onset are derived from the Australian visual impairment study(56). Progression probabilities for evolving from ME to SVL are derived from the Early Treatment Diabetic Retinopathy Study(62).

Risk adjustments for ME onset influenced by reduced HbA1c and systolic blood pressure are derived from the UKPDS 50(63) and UKPDS 36(64) (supplement 9). Racial risk adjustments are derived from the same American epidemiologic data as the retinopathy sub-model.(29)

The **Cataract** sub-model is comprised by three states: No cataracts, first cataract with operation and second cataract with operation. Probability of first cataract is derived from UKPDS data (58)and subsequent cataract probabilities are derived from a British publication of incidence and risk factors of cataract in diabetes outpatients(65). Risk adjustment for cataract onset influenced by 1% decrease in HbA1c is based on UKPDS data(45,66) (supplement 10).(29)

The **Nephropathy** sub-model is comprised by seven states: no renal complications, microalbuminuria (MA), gross proteinuria (GRP), end-stage renal disease (ESRD), hemodialysis (HD), peritoneal dialysis (PD), kidney transplant (RT) and death following ESRD.(29)
Probabilities for onset MA, progression from MA to GRP and progression from GRP to ESRD is dependent on ACE inhibitor treatment, and are derived from renal and diabetic renal studies(67-69). Progression from ESRD to renal transplant, death and dialysis, both PD and HD, is derived from a data report of chronic kidney disease and ESRD publication from the US National Institute of Diabetes, Digestive and Kidney Institute in 2010(70). Overview of all probabilities is available in supplement 11. Risk adjustments for HbA1c levels and systolic blood pressure are derived from the UKPDS 34 and the UKPDS 38 (13,14,19,48,71) (supplement 12).(29)

The **Hypoglycemia** sub-model is comprised by two states: alive and death due to hypoglycemia.
Hypoglycemic events are a great concern for diabetes patients. The hypoglycemia sub-model only factors in severe hypoglycemic events, which is defined as an event requiring assistance by a third party intervention. Naturally, only patients in the alive state can experience a severe hypoglycemic event. If the patient survives the hypoglycemic events it remains in the alive state and if the patient dies it switches to the death due to hypoglycemia state.(29)
Probabilities for severe hypoglycemic events is dependent of the medication received by the patient, hence different probabilities is applied for metformin, sulphonylurea and insulin derived from the UKPDS 33 study(58).(29)
The probability of a hypoglycemic event is adjusted for ACE inhibitor use, since this pharmaceutical class has been proven to improve the risk of severe hypoglycemic events due to elevated insulin sensitivity.

The **Lactic acidosis** sub-model is comprised by two states: alive and death due to lactic acidosis. The probability of a lactic acidosis event is derived from a 10-year literature review of lactic acidosis events and the risk of death is 43% post an acidosis event. Risk and probability is only applied to patients treated with metformin since they are the only patient group in risk of experiencing a lactic acidosis event(72).(29)

The **Non-specific mortality** sub-model is comprised of two states: alive or death. This sub-model captures probabilities of non-specific mortality distributed across age, gender and ethnicity, and are based on American data from 1999-2009 (73)due to lack of specific data for Denmark. Glucose lowering therapy and other diabetes related interventions are assumed to not be impacting non-specific mortality.(29)

Validation of the IMS CORE diabetes model

The IMS CORE diabetes model has been investigated for validation by comparing a total of 66 simulations against published study observations from studies used to build the model and observations from studies not used to build the model. This validation resulted in a goodness-of-fit value of R^2 = 0.9224. Hence, the simulation outcomes of the CORE diabetes model are likely to reflect diabetes progression and diabetic complications(29).

One-way sensitivity analysis

The complexity and lack of transparency of the model leads to difficulty in defining which parameters that is driving the results and has the greatest impact on the outcomes. Therefore, the base case was subjected to one-way sensitivity analyses with -20% and +20% changes in parameters suspected to be driving the outcomes: HbA1c reduction, hypoglycemic events and price of GLP-1 agonists. Both base case and one-way sensitivity analyses were simulated with 5000 patients over a 50-year timeframe.

RESULTS

The results of the probabilistic sensitivity analysis estimated that treatment with basal insulin + GLP-1 analogs was associated with a life expectancy of 11.989, discounted and undiscounted quality-adjusted life years of 6.1606 and 8.718. The estimated costs for direct, indirect and combined costs were 819547, 661485 and 1481032 DKK respectively.

Treatment with basal insulin + placebo was associated with a life expectancy of 11.981, discounted and undiscounted quality-adjusted life years of 6.069 and 8.634. The estimated costs associated with direct, indirect and combined costs were 797465, 662651 and 1460116 respectively. Full details can be seen in table 6 below.

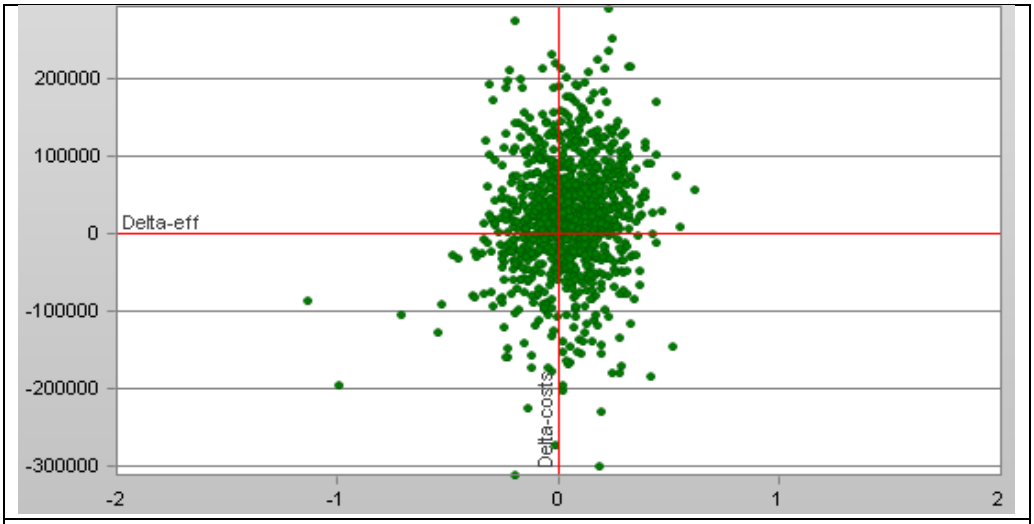
Table 6: Results of PSA analysis

	GLP-1 (mean)	GLP-1 (CI low)	GLP-1 (CI high)	Placebo (mean)	Placebo (CI low)	Placebo (CI high)
Life expectancy	**11.989**	11.849	12.128	**11.981**	11.850	12.113
Quality-adjusted life years	**6.106**	6.039	6.173	**6.069**	6.006	6.132
Undiscounted quality-adjusted years	**8.718**	8.590	8.846	**8.634**	8.515	8.754
Direct costs	**819547**	804364	834731	**797465**	782855	812076
Indirect costs	**661485**	601532	721437	**662651**	602459	722843
Combined costs	**1481032**	1405896	1556168	**1460116**	1385314	1534918

The result estimates for the compared treatments expressed in mean and 95% confidence intervals of the complete cohorts. All costs are DKK.

Treatment of type 2 diabetic patients uncontrolled on basal insulin + metformin with basal insulin in combination with GLP-1 analogs was estimated to be associated with an incremental increase of 0.037 QALYs and an incremental combined costs of 20916 DKK based on probabilistic sensitivity analysis of 1000 patients over a 50-year timeframe. These outputs were used to calculate the incremental cost-effectiveness ratio (ICER), which was estimated to 564333 DKK per quality-adjusted life year. Increased life expectancy was estimated to 0.007. From the ICER scatterplot in figure 4 it is evident that the ICERs is distribute quite even across the four quadrants, with a slightly higher density in the first quadrant. Quadrant one is more effective and more expensive, and in this case the majority is situated in the area with high extra costs and low QALY gain.

Figure 4: Incremental cost-effectiveness ratio scatterplot



ICER scatterplot showing the distribution of Δ combined costs/ ΔQALY

In table 7 the incremental costs associated with direct, indirect and combined costs together with confidence intervals are displayed. The incremental direct costs were estimated to 22082 DKK for treating patients with basal insulin + GLP-1 analog compared to basal insulin + placebo. Interesting the incremental indirect costs were estimated to be cost saving with a saving of 1166 DKK. Hence, if a national healthcare sector perspective were chosen instead of the present societal perspective the ICER would increase from 564333 DKK/QALY to 595796 DKK/QALY.

Table 7: Incremental costs, life expectancy and QALY

	Mean	CI low	CI high
Δ life expectancy	0.007	-0.014	0.028
Δ QALY	0.037	0.026	0.048
Δ direct costs	22082	19030	25134
Δ indirect costs	-1166	-4678	2345
Δ combined costs	20916	16162	25670
Δ direct costs / Δ QALY	595796	-927909	345805
Δ indirect costs / Δ QALY	-31463	-25370	1237714
Δ combined costs / Δ QALY	564333	-505289	1135530

Overview of the incremental life expectancy, quality-adjusted life years (QALY) and costs estimates associated with the compared treatments.

The CORE diabetes model allows for a breakdown of the total direct costs for the two compared treatment regiments as can be found in table 8. Direct treatment costs for basal insulin + GLP agonists was estimated to 177657 DKK compared to 168226 for basal insulin + placebo resulting in an incremental cost of 9431 DKK, which is due to the naturally more expensive pharmaceutical costs of the GLP-1 agonists compared to placebo. The estimated costs associated with management were close to equal. Hence, the medication costs were a major driver of the cost difference.

Table 8: Breakdown of direct costs

	GLP-1	Placebo
Total Costs	819547	797465
Treatment	177657	168226
Management	9758	9760

Cardiovascular disease	65462	66835
Renal	137415	131920
Ulcer/Amputation/ Neuropathy	215105	217610
Eye disease	122027	119025
Hypoglycemia	92124	84089
A detailed breakdown of the direct costs associated with the compared treatment regiments.		

The estimated costs associated with cardiovascular disease for basal insulin + GLP-1 agonists were 65462 DKK and 66835 DKK for basal insulin + placebo. The incremental costs of cardiovascular disease associated with GLP-1 agonists treatment was a cost saving of 1373 DKK. The difference in incidence of cardiovascular disease is suspected to be the driver of this incremental saving. Basal insulin + GLP-1 agonists were generally associated with a slightly lower incidence of congestive heart failure, peripheral vascular disease, angina, stroke and myocardial infarction compared to basal insulin + placebo, which contrary was associated with a slightly lower incidence of death due to congestive heart failure. A full overview can be found in supplement 10.
The costs related to renal disease was estimated higher in the cohort treated with basal insulin + GLP-1 agonists compared to basal insulin + placebo with 137415 DKK and 131920 DKK respectively. This difference of 5495 DKK is very likely to be caused by the increased incidence of renal diseases in the GLP-1 agonist treated cohort, as displayed in table 9 below.

Table 9: Cumulative incidence renal disease

	GLP-1 (mean):	GLP-1 (CI low):	GLP-1 (CI high):	Placebo (mean):	Placebo (CI low):	Placebo (CI high):
Microalbuminuria	31.831	31.410	32.252	31.177	30.761	31.594
Gross renal proteinuria	16.151	15.844	16.458	15.615	15.321	15.910
End-stage renal disease	6.348	6.178	6.518	6.065	5.908	6.223

The mean and confidence interval of the cumulative incidence of renal diseases.

The estimated costs with foot ulcer, amputation and neuropathy for basal insulin + GLP-1 agonists was associated with 215105 DKK and 217610 DKK for basal insulin + placebo. The incremental costs difference were due to a slightly lower incidence of foot ulcers and amputations (table 10) in the cohort treated with basal insulin + GLP-1 agonist. Contrary the incidence of neuropathy was slightly higher in the GLP-1 agonists cohort compared to the placebo cohort.

Table 10: Cumulative incidence of foot ulcer, amputation and neuropathy

	GLP-1 (mean):	GLP-1 (CI low):	GLP-1 (CI high):	Placebo (mean):	Placebo (CI low):	Placebo (CI high):
Ulcer	5.545	5.030	6.061	6.022	5.472	6.572
Recurrent ulcer	58.884	57.560	60.208	59.766	58.384	61.147
Amputation ulcer	9.559	9.292	9.826	9.767	9.488	10.046
Amputation recurrent ulcer	8.007	7.725	8.288	8.074	7.799	8.348
Neuropathy	59.716	59.105	60.327	59.203	58.611	59.796

The mean and confidence interval of the cumulative incidence of foot ulcer, recurrent foot ulcer, amputation as a consequences of foot ulcer, amputation as consequences of recurrent foot ulcer and neuropathy.

The estimated costs associated with eye diseases were 122027 and 119025 for basal insulin + GLP-1 agonists and basal insulin + placebo, respectively. The incremental cost of 3002 DKK was due to a slightly increased incidence of background diabetic retinopathy, macular edema, severe vision loss and cataract. A full overview can be found in supplement 11.

The direct costs estimates associated with hypoglycemic events were 92124 DKK for basal insulin + GLP-1 agonist and 84089 DKK for basal insulin + placebo, resulting in an incremental cost of 8035 DKK. The difference in costs was derived from the major hypoglycemic event incidence dissimilarities since minor hypoglycemic events were assumed to associated with no extra cost in the analysis.

Table 11: Incidence of hypoglycemic events per patient

	GLP-1 (mean):	GLP-1 (CI low):	GLP-1 (CI high):	Placebo (mean):	Placebo (CI low):	Placebo (CI high):
Major hypoglycemic event	6.427	6.311	6.543	6.030	5.921	6.138
Minor hypoglycemic event	444.997	436.603	453.391	440.137	432.265	448.009

The mean cumulative incidence and confidence intervals for the two compared treatments.

Results of one-way sensitivity analysis

A series of first order Monte Carlo sensitivity analysis and a base case was executed in order to investigate which factors that drive the model outcomes. The following parameters were subjected to -/+ 20% variation: HbA1c reduction, hypoglycemic event rate and price of GLP-1 agonists.

Treatment with GLP-1 agonists was in the base case associated with increased life expectancy of 0.046 years, increased QALY of 0.090 and increased costs compared to placebo treatment.

HbA1c reduction sensitivity analyses showed that HbA1c plays a major role in the outcomes of the model. Hence, a -20% reduction of the HbA1c reduction resulted in a significantly decreased ΔQALY from 0.090 in the base case to 0.029 in the sensitivity analysis. The Δ direct costs decreased with almost half compared to the base case, this is suspected to be due to a lower hypoglycemic event rate.

Additional 20% HbA1c reduction resulted in increased Δ life expectancy but a small decrease in Δ QALY, which potentially can be explained with the increased likelihood of hypoglycemic events that tight glycemic control conveys. The decreased Δ direct costs are most likely caused by a decreased incidence of diabetes complications with exception of hypoglycemic events, which would be expected to increase. Similar the Δ indirect costs decrease is suspected to driven by the reduced incidence of diabetes complications and subsequent decreased absenteeism.

Sensitivity analyses of the hypoglycemic event rate showed that the Δ QALY was reduced in both analyses compared to the base case, which is interesting since a decrease in hypoglycemic event rate would be suspected to increase the Δ QALY. A 20% reduction of the hypoglycemic event rate plays a major impact on the Δ direct cost which were nearly reduced to zero, but contrary did a 20% increase of the hypoglycemic event rate not increase the Δ direct costs, in fact it slightly decreased compared to the base case. The Δ indirect costs were also impacted by +/- 20% variation of the hypoglycemic event rates. The 20% reduction resulted in an increase in Δ indirect costs and the 20% increase of events resulted in a reduction in Δ indirect costs.

Table 12: One-way sensitivity analyses of HbA1c reduction and hypoglycemic events

	Base case	HbA1c reduction		Hypoglycemic event rate	
		-20%	+20%	-20%	+20%
Δ life expectancy	0.046	-0.055	0.098	-0.031	0.007
Δ QALY	0.090	0.029	0,117	0.084	0.064
Δ direct costs	17576	-811	371	-22240	13117
Δ indirect	2300	8291	-4934	4728	-184

costs					
Δ combined costs	19876	7479	-4563	-17512	12933
Δ direct costs / Δ QALY	195985	-28277	3167	-264617	203843
Δ indirect costs / Δ QALY	25645	288961	-42107	56251	-2853
Δ combined costs / Δ QALY	221630	260684	-38940	-208366	200990
Impact -/+ variation of HbA1c reduction and hypoglycemic event rate. Direct, indirect and combined costs are expressed in DKK.					

One-way sensitivity analyses of the GLP-1 agonists price was undertaken with +/- 20% variation. A 20% reduction of GLP-1 price only impacted the Δ direct costs with a reduction from 17576 DKK in the base case to 1947 DKK. The subsequent ICERs were 21715, 25645 and 47361 DKK per QALY for direct costs/QALY, indirect costs/QALY and combined costs/QALY respectively.
A 20% increase of GLP-1 analog price showed an impact on the Δ direct price, which increase from 17576 DKK in the base case to 33205 DKK. Interesting the impact of the increased GLP-1 analog price had a lower impact on the Δ direct costs compared to the reduction of GLP-1 analog price.

Table 13: One-way sensitivity analysis of GLP-agonists price

	Base case	GLP-1 agonist price	
		-20%	+20%
Δ life expectancy	0.046	0.046	0.046
Δ QALY	0.090	0.090	0.090
Δ direct costs	17576	1947	33205
Δ indirect costs	2300	2300	2300
Δ combined costs	19876	4247	35505
Δ direct costs / Δ QALY	195985	21715	370255
Δ indirect costs / Δ QALY	25645	25645	25645
Δ combined costs / Δ QALY	221630	47361	395900
One-way sensitivity analysis of the GLP-1 agonist price impact. All costs are expressed in DKK			

DISCUSSION

Results from the probabilistic sensitivity analysis showed a quite high ICER that was above the generally accepted threshold of 250000 DKK per gained QALY, but the one-way sensitivity analyses showed that small changes in the key parameters could affect the outcome quite substantial. Scrutinizing the data input might give an answer to why the resulting ICER was estimated above the threshold.
The two randomized trials used in the analysis showed somewhat diverging results, as described earlier, in weight reduction and hypoglycemic event rates. Especially the diverging reported results in hypoglycemic event rates are affecting the outcome of the present analysis. As earlier described *Riddle et al*. 2013(12) reported 4.8 severe hypoglycemic events per 100 patient years in the lixisenatide cohort

while *Buse et al*. 2011(18) only reported severe hypoglycemic events in the placebo cohort, 2.46 per 100 patient years. The tendency in retrospective studies have reported a lower incidence of severe hypoglycemic events in cohorts treated with GLP-1 agonists compared to cohorts only treated with insulin according to a review of studies published by *Holst & Vilsbøl*(6). This effect might be due to the decreased insulin dosage in the GLP-1 agonists treatment cohorts and the increased demand for higher dosage of basal insulin to maintain glycemic control. According to the one-way sensitivity analysis of hypoglycemic event rate the direct costs are highly sensitive to a reduction of the hypoglycemic event rate and subsequent impacts the cost-effectiveness ratio. Outcomes of the individual trials in a cost-effectiveness analysis could be interesting to compare with the outcome of the present analysis. In Eli Lilly's cost-effectiveness analysis submitted to the Scottish Medicine Consortium (SMC), the combination of basal insulin and exenatide showed an ICER of 16000 GBP (approx. 147200 DKK) based on an incremental QALY of 0,183 and incremental costs of 1721 GBP (approx.15833 DKK) over 20 years. When comparing to the one-way sensitivity analysis this result seems obtainable and realistic in the light of the slightly higher HbA1c reduction in the study by *Buse et al.* 2011(18).
The cost of GLP-1 agonists was composed by the combined mean of liraglutide, exenatide and lixisenatide although the treatment outcomes results only are derived from exenatide and lixisenatide studies. Liraglutide have been shown to be slightly more effective than lixisenatide and exenatide in cohorts treated with metformin monotherapy. Hence, a minimal price premium is added to the mean price of GLP-1 agonists without the potential clinical effect of the drug.
In *Riddle et al*. 2013(12) the baseline insulin treatment consisted of various insulin which was not captured in the insulin treatment costs as insulin glargine was used as basal insulin in the analysis in both cohorts. The costs of basal insulin were equal in both cohorts hence not affecting the incremental cost-effectiveness ratio, but in future analyses the detailed insulin costs should be used for a more representative analysis.
A great proportion of the quality of life values, probabilities and risk ratios were derived other countries than Denmark, and some were of older date. Therefore these values might not accurate reflect the reality for the current Danish population, but in the case that no literature was available specific for Denmark, studies from other population was applied.

Both cohorts were assumed to maintain their respective treatment of basal insulin + GLP-1 agonist or basal insulin + placebo for 5 years before switching to an insulin intensification of basal insulin together with mealtime insulin. This assumption was based on published clinical inertia in patients treated with oral anti-diabetics. According to advice from the Scottish Medicine Consortium (SMC) regarding exenatide in combination with basal insulin the SMC experts commend that a more clinical representative estimate would be that patients remains on the treatment for 3 years, but does also list 5 years as an acceptable timeline.
The effect of weight loss in diabetes on clinical parameters, and which level of weight loss that is clinical significant have been discussed and disputed. Some evidence suggest that a weight loss above 10% have a positive impact on glycemic control, blood pressure and blood lipid composition(66). Weight loss associated with GLP-1 agonists was estimated to 1.79 kg from the two studies, which is not near a 10% reduction of body weight. Therefore it can be questioned whether the society should pay for a weight reduction with doubtful clinical impact.

In order to account for all the complications related to diabetes in the estimation of the cost-effectiveness the IMS CORE Diabetes model includes a great number of transition probabilities, regression formulas, algorithms and risks associated with both treatment and diabetic complication parameters. This result in great complexity and difficulties in comprehending which parameters actually affects which sub-models and the final outcomes. Furthermore, the transparency of the model is very limited due to the model setup, hence the user is unable to check the calculation engine and therefore only the input and output are available for scrutiny. This is also known as a black-box issue.

Thus, one could speculate why the IMS CORE Diabetes model should be applied in the modeling of long-term outcomes in diabetes. The model has been used widely used, as over 80 articles have been published in peer-review journals (IMS CORE diabetes website). Furthermore, it has been validated against epidemiological studies as earlier described and further validated against other diabetes specific models in the recurrent Mount Hood challenge, which is a congress or forum for diabetes health economic modelers allowing each model to compare the predicted results of a specific modeling task with the other diabetes models at which the CORE Diabetes model perform well(67).
Another criticism of the model is that a great deal of the algorithms used in the model are derived from studies executed several years ago and therefore not reflecting the outcomes of more modern treatments e.g. the UKPDS where started in 1977 and finished in 1997, hence the benefits from newer interventions such as long acting basal insulin, DPP-4 inhibitor, SLGT-2 and GLP-1 agonist are not captured in these algorithms. This criticism has been addressed by updating the algorithms via retrospective follow-up studies.

Comparator in the current analysis was basal insulin + placebo based on the tendencies from published studies of clinical inertia in clinical practice showing that patients rather start an additional oral anti-diabetic agent rather than intensifying the treatment(19). On this basis placebo was chosen as comparator in order to reflect the clinical reality. Future analyses ought to include DPP-4 inhibitor, which mimics the actions of GLP-1 agonists although with lower efficacy but at a lower price. Furthermore, the new pharmaceutical class SLGT-2 could interesting to include into a more elaborate meta-analysis since this class have shown promising results in terms of HbA1c reduction and weight loss.
A comparison against basal-bolus comprised of basal insulin and once daily injection of bolus insulin would also make an interesting comparator since the HbA1c reduction probably would greater but so would the weight gain and hypoglycemic risk.

CONCLUSION

Based on the subsequent analysis in patients in poor control on existing treatment of basal insulin + metformin with a 50 years time horizon, the addition of a non-brand specific GLP-1 agonist to an existing basal insulin treatment is not cost-effective in comparison to remaining on basal insulin treatment. Although, the sensitivity analysis showed indications of feasibility of the treatment regiment if the clinical trials was not combined. Hence, a final conclusion is possible to be concluded. Further research is required in order to make a final conclusion.

SUPPLEMENTS

Supplement 1:

Days off work (DoW)	Days	Reference:
Cardiovascular disease		
Myocardial infarction event	54	(74)
Annual DoW Myocardial infarction	19	(74)
Onset angina	55	(74)
Annual DoW angina	15	(74)
DoW, onset CHF	73	(74)
annual DoW, CHF	6	(74)
DoW, stroke event	88	(74)
annual DoW, stroke	34	(74)
DoW, onset PVD	65	(74)
annual DoW PVD	20	(74)
RENAL DISEASE		
DoW, Onset HD	79	(74)
DoW, Onset PD	0	No data
DoW, Onset RT	0	No data
annual DoW, HD	21	(74)
annual DoW, PD	0	No data
annual DoW, RT	0	No data
EYE DISEASE		
DoW, onset SVL	0	No data
annual DoW, SVL	0	No data
DoW, onset cataract	0	No data
annual DoW, cataract	0	No data
NEUROPathy /PVD/FOOT ULCER/AMP		
DoW, onset neuropathy	45	(74)
annual DoW neuropathy	17	(74)
DoW, onset ulcer	83	(74)
annual DoW, ulcer	46	(74)
DoW, onset infected ulcer	46	(74)
annual DoW, infected ulcer	10	(74)
DoW, onset healed ulcer	0	No data
annual DoW,healed ulcer	0	No data
DoW, onset gangrene	0	No data
annual DoW, gangrene	0	No data
DoW, amputation event	104	(74)
annual DoW, amputation	36	(74)

DAYS OFF WORK (DOW) ACUTE EVENTS		
DoW major hypo	6.6	(75)
DoW lactic acid event	0	No data

Supplement 2:

Costs associated with management of diabetes complications (medication, procedures and consultation by healthcare professional):

Description	Values	Units	Year	Reference:
Annual cost for statin treatment (applied if patient on 1º or 2º prevention)	151,11	DKK	2014	www.medicinpriser.dk April 2014
Annual cost for aspirin treatment (applied if patient on 1º or 2º prevention)	188,34	DKK	2014	www.medicinpriser.dk April 2014
Annual cost for ACE inhibitor treatment (applied if patient on 1º or 2º prevention)	91,98	DKK	2014	www.medicinpriser.dk April 2014
Annual cost for microalbuminuria screening (applied if patient is screened)	175,38	DKK	2013	(76) Only available in Danish. Inflated from 2003 price 145,55 DKK to 2013 175,38 DKK price via dst.dk
Annual cost for gross proteinuria screening (applied if patient is screened)	92,55	DKK	2013	(76) Only available in Danish. Inflated from 2003 price 92,55 DKK to 2013 112,29 DKK price via dst.dk
Event cost if suffering to side effects from ACE inhibitors	133,84	DKK	2014	www.laeger.dk
Cost for eye screening (assumed annual)	453,29	DKK	2014	Tariffs for specialist
Cost for foot care program (annual cost applied monthly, i.e. cost/12)	303,00	DKK	2013	(76) Only available in Danish.
Cost of non-standard ulcer treatment (monthly)	133,84	DKK	2014	www.laeger.dk

Cost for ant-depression treatment	54,75	DKK	2014	www.medicinpriser.dk April 2014
Cost for office-based questionnaire for presence of depressive symptoms	206,48	DKK	2014	Tariffs for GPs available at www.laeger.dk/
Cost for myocardial infraction event	58.477,17	DKK	2014	wwww.drg.dk 2014, www.medicinpriser.dk and www.pro.medicin.dk
Cost for myocardial infarction in all subsequent years following event	477,42	DKK	2014	www.medicinpriser.dk and www.pro.medicin.dk
Cost for angina event (all costs incurred in first year)	12.448,42	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Cost for angina in all subsequent years following event	477,42	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Cost for congestive heart failure event (all costs incurred in first year)	77.919,62	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Cost for congestive heart failure in all subsequent years following event	269,37	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Cost for stroke event (all costs incurred in first year)	127.553,25	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Cost for stroke in all subsequent years following event	29.112,25	DKK	2013	(77)
Costs incurred with stroke event if subject dies within 30 days	98.441,00	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Cost for peripheral vascular disease event (all costs incurred in first year)	24.053,00	DKK	2014	www.drg.dk

Cost for peripheral vascular disease in all subsequent years following event (atherosclerosis of the vessels)	4.094,52	DKK	2013	(78)
Annual cost for dialysis in first year (no differentiation between PD and HD)	408.686,57	DKK	2013	(76) Only in Danish.
Annual cost for dialysis in second year (no differentiation between PD and HD)	408.686,57	DKK	2013	(76) Only in Danish.
Annual cost for dialysis in first year (no differentiation between PD and HD)	320.476,01	DKK	2013	(76) Only in Danish.
Annual cost for dialysis in second year (no differentiation between PD and HD)	320.476,01	DKK	2013	(76) Only in Danish.
Annual costs for renal transplant for year of transplant	233.741,84	DKK	2014	www.drg.dk, www.medicinpriser.dk and www.pro.medicin.dk
Annual costs for all years following successful renal transplant	23.219,84	DKK	2014	www.medicinpriser.dk and www.pro.medicin.dk
Event cost for a "major" hypoglycemic event	23.784,00	DKK	2014	www.drg.dk
Event cost for a "minor" hypoglycemic event	0,00	DKK	2010	Minor events are considered not to require health care resources
Cost for a lactic acidosis event	23.784,00	DKK	2014	www.drg.dk
Cost for edema as an adverse event associated with therapy at onset and for the first year (GP visit)	133,84	DKK	2014	Assumed to cover one GP visit. Tariffs for GPs available at www.laeger.dk

Cost of edema follow–up assumed not to require medical resource consumption once medication is changed	0,00	DKK	NA	
Cost for laser treatment/retinal photocoagulation	2.804,00	DKK	2014	www.drg.dk
Cost for first or second cataract extraction in the first year	7.785,50	DKK	2014	www.drg.dk
Cost for all years following cataract extraction	457,46	DKK	2013	Speciallæge overenskomster, kapitel 17, Ydelse nummer 0110 DKK 228,73
Cost of blindness in the first year only	84.928,85	DKK	2013	(76) Only available in Danish.
Cost of blindness in all subsequent years	84.928,85	DKK	2013	(76) Only available in Danish.
Cost of neuropathy in the first year	24.401,00	DKK	2014	www.drg.dk
Cost of neuropathy in all subsequent years	512,46	DKK	2014	www.medicinpriser.dk April 2014
Cost of amputation event (all medical costs except prosthesis)	142.136,00	DKK	2014	www.drg.dk
Cost of prosthesis following amputation event	13.134,57	DKK	2013	(79)
Cost of gangrene treatment	16.942,94	DKK	2013	(79)
Cost for healed ulcer, i.e. history of ulcer only	44.798,97	DKK	2013	(80)
Cost for treatment of infected ulcer	104.966,00	DKK	2014	www.drg.dk
Cost for treatment of an uninfected ulcer	104.966,00	DKK	2014	www.drg.dk

Cost for maintenance therapy of amputation event as a result of an ulcer	152.401,34	DKK	2013	(80)

Supplement 3:

Transition probabilities for the myocardial infarction and myocardial infarction mortality sub-model:

Myocardial Infarction (MI)	**Value**	**Type**	**Comments**	**Reference**
Prop. initial congestive heart disease event myocardial infraction Female	0,361	[0-1]	Table 2	(42)
Prop. Initial congestive heart disease event myocardial infraction Male	0,522	[0-1]	Table 2	(42)
Prop. subsequent congestive heart disease event myocardial infraction female	0,474	[0-1]	Table 2	(42)
Prop. subsequent congestive heart disease event myocardial infraction Male	0,451	[0-1]	Table 2	(42)
Increased risk myocardial infraction if microalbuminuria	1,00	Multiplier	No data available thus no adjustment is applied	No data
Increased risk myocardial infraction if gross proteinuria	1,00	Multiplier	No data available thus no adjustment is applied	No data
Increased risk myocardial infraction if end-stage renal disease	1,00	Multiplier	No data available thus no adjustment is applied	No data
Multiplier Aspirin 1° myocardial infraction	0,82	Multiplier	Figure 3 - Major coronary event	(51)
Multiplier Aspirin 2° myocardial infraction	0,80	Multiplier	Figure 3 - Major coronary event	(51)
Multiplier Statins 1° myocardial infraction I	0,70	Multiplier	Figure 2 - Major coronary events	(52)
Multiplier Statins 2° myocardial infraction	0,81	Multiplier	Table 2 - Coronary heart disease death or non-fatal myocardial infarction	(81)
Risk Reduct with ACE 1st myocardial infraction	0,78	[0-1]	Table 3 - Primary outcome MI	(53)
Risk Reduct with ACE rect myocardial infraction	0,78	[0-1]	Table 3 - Primary outcome MI	(53)
MI mortality	**Value**	**Type**	**Comments**	**Reference**

p sudden death 1st MI male	0,393	[0-1]	Table 2 - Case fatality before admission	(40)
p sudden death 1st MI female	0,364	[0-1]	Table 2 - Case fatality before admission	(40)
p sudden death rec MI male	0,393	[0-1]	Table 2 - Case fatality before admission	(40)
p sudden death rec MI female	0,364	[0-1]	Table 2 - Case fatality before admission	(40)
Multiplier 12 month mortality MI convent treatment	1,45	Multiplier	p.61 - The relative reduction in mortality was 31% with the Cox model	(82)
Multiplier Aspirin mortality 1st year MI	0,88	Multiplier	Figure 4d - Death from any cause - Prior MI - "0.88"	(83)
Multiplier Aspirin mortality 2nd+ years MI	0,88	Multiplier	Figure 4d - Death from any cause - Prior MI - "0.88"	(83)
Multiplier Statins mortality 1st year MI	0,75	Multiplier	Table 4	(84)
Multiplier Statins mortality 2nd+ years MI	1,00	Multiplier	No data available thus no adjustment is applied	No data
Multiplier Aspirin sudden death MI	1,00	Multiplier	No data available thus no adjustment is applied	No data
Multiplier Statin sudden death MI	1,00	Multiplier	Pooled analysis of four month follow-up data from ten trials.	(85)
Multiplier ACE sudden death MI	1,00	Multiplier	No data available thus no adjustment is applied	No data
Risk Reduct with ACE MI long-term mort	0,64	[0-1]	Treatment with trandolapril resulted in a relative risk (RR) of death from any cause for the diabetic group of 0.64 (95% confidence interval 0.45 to 0.91)	(86)

Supplement 4:

Transition probabilities for the stroke sub-model:

Stroke	Value	Type	Comments	Reference
Multiplier Aspirin 1st stroke	0,86	Multiplier	Figure 3 - Ischaemic stroke	(51)
Multiplier Aspirin 2nd stroke	0,78	Multiplier	Figure 3 - Ischaemic stroke	(51)
Multiplier Statins 1st stroke	0,81	Multiplier	Figure 2 - Major cerebrovascular events	(52)
Multiplier Statins 2nd stroke	0,84	Multiplier	Table 2 - Nonfatal or fatal stroke on atorvastatin 80 mg per day	(87)

Risk Reduct with ACE 1st stroke	0,67	[0-1]	Table 3 - Primary outcome stroke	(53)
Risk Reduct with ACE rec stroke	0,72	[0-1]	4 years of follow up study on reduction blood pressure	(88)
Stroke mortality	**Value**	**Type**	**Comments**	**Reference**
p 30-day death 1st stroke male	0,124	[0-1]	Table 4	(50)
p 30-day death 1st stroke female	0,124	[0-1]	Table 4	(50)
p 30-day death rec stroke male	0,422	[0-1]	Recurrent strokes were fatal within 30 days in 57 cases (out of 135 patients)	(50)
p 30-day death rec stroke female	0,422	[0-1]	Similar to the male sub-group	(50)
Multiplier Aspirin mortality 1st year stroke	0,84	Multiplier	Figure 4d - Death from any cause prior stoke	(83)
Multiplier Aspirin mortality 2nd+ years stroke	0,84	Multiplier	Figure 4d - Death from any cause prior stoke	(83)
Multiplier Statins mortality 1st year stroke	1,00	Multiplier	Cochrane Analysis; Analysis 1.2 - Despite the reduction in serious cardiovascular events with statin therapy, there was no evidence that intervention reduced all-cause mortality in patients with a history of stroke	(89)
Multiplier Statins mortality 2nd+ years stroke	1,00	Multiplier	Cochrane Analysis; Analysis 1.2 - Despite the reduction in serious cardiovascular events with statin therapy, there was no evidence that intervention reduced all-cause mortality in patients with a history of stroke	(89)
Multiplier Aspirin sudden death stroke	0,95	Multiplier	Aspirin 160-300 mg daily within 48 hours of ischemic stroke	(90)
Multiplier Statin sudden death stroke	1,00	Multiplier	Pooled analysis of four-month follow-up data from 10 trials.	(85)
Multiplier ACE sudden death stroke	0,49	Multiplier	Previous use of ACEIs was associated with a reduced risk of death within 28 days of stroke.	(91)

Risk reduction with ACE stroke long-term mortality	1,000	[0-1]	Prescription of ACE inhibitors was not associated with reduced risk of death.	(92)
Risk reduction with ACE stroke 12 month mortality	1,000	[0-1]	Prescription of ACE inhibitors was not associated with reduced risk of death.	(92)

Supplement 5:

Transition probabilities for the foot ulcer and amputation sub-model

Angina	Value	Type	Comments	Reference
Prop. init CHD event angina Female	0,621	[0-1]	Table 2 - combination of angina pectoris and coronary insufficiency	(42)
Prop. init CHD event angina Male	0,420	[0-1]	Table 2 - combination of angina pectoris and coronary insufficiency	(42)
Prop. subseq CHD event angina Female	0,359	[0-1]	Table 2 - combination of angina pectoris and coronary insufficiency	(42)
Prop. subseq CHD event angina Male	0,301	[0-1]	Table 2 - combination of angina pectoris and coronary insufficiency	(42)
mult Angina MA	1,00	Multiplier	No data available thus no adjustment is applied	No data
mult Angina GRP	1,00	Multiplier	No data available thus no adjustment is applied	No data
mult Angina ESRD	1,00	Multiplier	No data available thus no adjustment is applied	No data

Supplement 6:

Probabilities for neuropathy onset:

Neuropathy	Value	Type	Comment	Reference
p onset neuropathy - type 2 baseline	0,0190	[1-0]	Risk for neuropathy onset at zero years of diabetes duration	(47)
p onset neuropathy - type 2 10 years	0,0695	[1-0]	Risk for neuropathy onset at ten years of diabetes duration	(47)

Supplement 7:

Transition probabilities for the foot ulcer and amputation sub-model

Foot ulcer and amputation	Value	Type	Comment	Reference

p gangrene to amp with gang	0,181800	[0-1] monthly based	Table 1 - Gangrene > Amputation > Gangrene	(54)
p gangrene to healed amp	0,308200	[0-1] monthly based	Table 1 - Gangrene > Amputation > Healed, History of Amputation	(54)
p death following onset gangrene	0,009800	[0-1] monthly based	Table 1 - Gangrene > Deceased	(54)
p death with history amputation	0,004000	[0-1] monthly based	Table 1 - Healed Ulcer, History of Amputation > Deceased	(54)
p death following healed ulcer	0,004000	[0-1] monthly based	Table 1 - Healed Ulcer > Deceased	(54)
p developing recurrent uninfected ulcer	0,039300	[0-1] monthly based	Table 1 - Healed Ulcer > Uninfected Ulcer	(54)
p amputation following infected ulcer	0,003700	[0-1] monthly based	Table 1 - Infected Ulcer > Amputation > Infected Ulcer	(54)
p infect ulcer->amp healed	0,044500	[0-1] monthly based	Table 1 - Infected Ulcer > Amputation Healed Ulcer, History of Amputation	(54)
p infect ulcer->death	0,009800	[0-1] monthly based	Table 1 - Infected Ulcer > Deceased	(54)
p infect ulcer->gangrene	0,007500	[0-1] monthly based	Table 1 - Infected Ulcer > Gangrene	(54)
p infect ulc->uninfect ulc	0,139700	[0-1] monthly based	Table 1 - Infected Ulcer > Uninfected Ulcer	(54)
p recurrent amp	0,008451	[0-1] monthly based		(54)
p uninfect ulc->death	0,004000	[0-1] monthly based	Table 1 - Uninfected Ulcer > Deceased	(54)
p uninfect ulc->infect ulc	0,047300	[0-1] monthly based	Table 1 - Uninfected Ulcer > Infected Ulcer	(54)
p uninfect ulc->healed ulc	0,078700	[0-1] monthly based	Table 1 - Uninfected Ulcer > Healed Ulcer	(54)
p developing ulcer with neither neur or PVD	0,000250	[0-1] monthly based	Table 1 - No foot ulcer > uncomplicated foot ulcer (Risk 1)	(55)

p developing ulcer with either neur or PVD	0,006092	[0-1] monthly based	Table 1 - No foot ulcer > uncomplicated foot ulcer + deep foot infection (Risk 2)	(55)
p developing ulcer with both neur or PVD	0,006092	[0-1] monthly based	Table 1 - No foot ulcer > uncomplicated foot ulcer + deep foot infection + foot ulcer and critical ischemia (Risk 3)	(55)

Supplement 8:

Transition probabilities for the congestive heart failure sub-model

Congestive heart failure	Value	Type	Comments	Reference
Increased risk HF if MAU	1,00	Multiplier	No data available thus no risk is applied	No data
Increased risk HF if GPR	1,00	Multiplier	No data available thus no risk is applied	No data
Increased risk HF if ESRD	1,00	Multiplier	No data available thus no risk is applied	No data
Risk reduct HF if Aspirin	1,00	[0-1]	No data available thus no risk is applied	No data
Risk reduct HF if Statin	1,00	[0-1]	No data available thus no risk is applied	No data
Risk reduct HF if ACE	0,80	[0-1]	Table 3 - Any heart failure on ramipril (10 mg per day)	(53)
Risk reduct HF death if ACE	0,80	[0-1]	The administration of ACE inhibitors in patients with HF due to left systolic dysfunction leads to statistically and clinically significant reductions in mortality (20 to 23%)	(93)
Multiplier HF death diab male	1,00	Multiplier	Table 6	(44)
Multiplier HF death diab female	1,70	Multiplier	Table 6	(44)

Supplement 9:

Transition probabilities for the eye disease sub-models:

Eye disease transition probabilities	Value	Type	Comments	Reference
p onset of BDR - type 2	0,0229	[0-1]	- Table 2	(56)

p BDR to PDR - type 2	0,0202	[0-1]	- Table 2	(56)
p PDR to SVL - laser therapy - type 2	0,0284	[0-1]	- Table 2 (Xenon DRS)	(57)
p PDR to SVL - no laser therapy - type 2	0,0798	[0-1]	- Table 2 (Xenon DRS)	(57)
p onset ME	0,0165	[0-1]	- p339	(56)
p ME to SVL - no laser - type 2	0,0874	[0-1]	- p1799	(62)
p ME to SVL - laser - type 2	0,0417	[0-1]	- p1799	(62)
p onset of cataract extraction - male - type 2	0,0056	[0-1]	- Figure 4 - Intensive arm	(58)
p onset of cataract extraction - female - type 2	0,0056	[0-1]	- Figure 4 - Intensive arm	(58)
p recurrent cataract extraction - male - type 2	0,0080	[0-1]	- p19	(65)
p recurrent cataract extraction - female - type 2	0,0136	[0-1]	- p19	(65)
Risk Reduct with ACE BDR T2	0,75	[0-1]	Assumed same benefit as per type 1 diabetes	(60)
Risk Reduct with ACE PDR T2	0,19	[0-1]	Assumed same benefit as per type 1 diabetes	(60)
Risk Reduct with ACE ME T2	1,00	[0-1]		No data
Risk Reduct with ACE SVL T2	1,00	[0-1]		No data
mult race Hisp no->BDR T2	1,44	multiplier	Table 4	(94)
mult race Black no-	1,57	multiplier	Table 4	(94)

>BDR T2				
mult race Am Ind no->BDR T2	1,20	multiplier	Table 1	(61)
mult race Hisp BDR->PDR T2	1,44	multiplier	Table 4	(94)
mult race Black BDR->PDR T2	1,57	multiplier	Table 4	(94)
mult race AM Ind BDR->PDR T2	1,20	multiplier	Table 1	(61)
mult race Hisp PDR->SVL T2	1,00	multiplier		No data
mult race Black PDR->SVL T2	1,00	multiplier		No data
mult race AM Ind PDR->SVL T2	1,00	multiplier		No data
mult race Hisp ME->SVL T2	1,00	multiplier		No data
mult race Black ME->SVL T2	1,00	multiplier		No data
mult race AM Ind ME->SVL T2	1,00	multiplier		No data
risk reduct for 1%-point lower HbA1c Cataract T2	0,19	[0-1]	Table 3 - based on updated mean HbA1c - versus comparator value of 7.1%	(45)

Supplement 10:

Transition probabilities for the kidney disease sub-model

Kidney disease	Values	Type	Comments	Reference
p onset MA - type 2 - no ACE	0,03451	[0-1]	6-year follow-up transition to MA	(95)
p onset MA - type 2 - ACE	0, 02085	[0-1]	Risk ratio of 0.60 for ACE inhibitors versus placebo/no treatment for the transition to microalbuminuria from normoalbuminuria based on MA of 6 trials	(69)
p MA to GRP - type 2 - no ACE	0, 10322	[0-1]	Over a 5-year follow-up, the risk of proteinuria was 42% in the placebo group	(96)

p MA to GRP - type 2 - ACE	0,04784	[0-1]	Risk ratio of 0.45 for ACE inhibitor versus placebo/no treatment for the transition to GRP from microalbuminuria based on MA of 17 trials	(69)
p GRP to ESRD - type 2 - no ACE	0,091	[0-1]	9.1 events per 100 patient-years in the placebo group of the RENAAL trial	(97)
p GRP to ESRD - type 2 - ACE	0,05563	[0-1]	Risk ratio of 0.60 for ACE inhibitor versus placebo/no treatment for the development of end-stage kidney disease based on MA of 10 trials	(69)
Prop ESRD - HD treatment	Current age	[0-1]	0,0.4901; 20,0.8343; 45,0.8864; 65,0.9223; 75,0.9596 - Table 4a(ii), p280 (usage at 90-days following RRT onset)	(98)
Prop ESRD - PD treatment	Current age	[0-1]	0,0.3168; 20,0.0988; 45,0.0736; 65,0.0588; 75,0.0388 - Table 4a(ii), p280 (usage at 90-days following RRT onset)	(98)
Prop ESRD - RT treatment	Current age	[0-1]	0,0.1931; 20,0.0669; 45,0.0400; 65,0.0169; 75,0.0016 - Table 4a(ii), p280 (usage at 90-days following RRT onset)	(98)
p die ESRD under HD treatment	Current age	[0-1]	0,0.1550 - Figure 6.9(ii), p307	(98)
p die ESRD under PD treatment	Current age	[0-1]	0,0.1780 - Figure 6.9(ii), p307	(98)
p die ESRD after RT	Current age	[0-1]	0,0.0223 - Figure 7.34(ii), p320	(98)

Supplement 11:

Quality of Life Utilities	Mean	Utility/ Disutility	Comments	Reference
QoL T2 no complications	0,8140	[0-1]	Table 2 - Tobit regression values	(32)
QoL MI event	-0,1290	[-1-0]	Table 2 - Tobit regression values	(32)
QoL post MI	0,7360	[0-1]	Table 2 - Tobit regression values	(32)
QoL angina	0,6820	[0-1]	Table 2 - Tobit regression values	(32)
QoL CHF	0,6330	[0-1]	Table 2 - Tobit regression values	(32)
QoL stroke event	-0,1810	[-1-0]	Table 2 - Tobit regression values	(32)
QoL post Stroke	0,5450	[0-1]	Table 2 - Tobit regression values	(32)

QoL PVD	0,5700	[0-1]	Appendix A - #535	(35)
QoL MA	0,8140	[0-1]	No data. Therefore assumed QoL as T2 without complications	
QoL GRP	0,8140	[0-1]	No data. Therefore assumed QoL as T2 without complications	
QoL HD	0,6040	[0-1]	Table 2	(99)
QoL PD	0,6120	[0-1]	Table 2	(99)
QoL RT	0,7500	[0-1]	Appendix A - #742	(35)
QoL BDR	0,7900	[0-1]	Table 3	(34)
QoL BDR wrongly treated	0,7900	[0-1]	Table 3	(34)
QoL PDR laser treated	0,7900	[0-1]	Table 3	(34)
QoL PDR no Laser	0,7900	[0-1]	Table 3	(34)
QoL ME	0,7900	[0-1]	Table 3	(34)
QoL SVL	0,6700	[0-1]	p.621	(33)
QoL cataract	0,6200	[0-1]	p.215	(100)
QoL neuropathy	0,6300	[0-1]	p.621	(33)
QoL heal ulcer	0,8140	[0-1]	No data. Therefore assumed QoL as T2 without complications	
QoL active ulcer	0,7500	[0-1]	Table 4	(101)
QoL amp event	-0,5380	[-1-0]	Table 2 - Tobit regression values	(32)
QoL post amputation	0,4020	[0-1]	Table 2 - Tobit regression values	(32)
QoL for major hypo events	-0,0118	[-1-0]	Based on events in past 3 months	(36)
QoL for minor hypo events	-0,0035	[-1-0]	Based on events in past 3 months	(36)
QoL LA event	0,0000	[-1-0]	No data. Therefore assumed disutility of 0	
QoL fear of hypoglycemic event	0,0000	[-1-1]	No data. Therefore assumed disutility of 0	
QoL edema event (adv.ev.)	0,0000	[-1-0]	No data	

QoL post edema (adv.ev.)	0,8140	[0-1]	No data. Therefore assumed QoL as T2 without complications	

Supplement 12:

Table : Cumulative incidence cardiovascular disease (in %)

	GLP-1 (mean)	GLP-1 (CI low)	GLP-1 (CI high):	Placebo (mean):	Placebo (CI low):	Placebo (CI high):
Congestive heart failure death	26.679	26.095	27.264	26.332	25.752	26.913
Congestive heart failure event	14.780	13.891	15.669	16.023	15.095	16.952
Peripheral vascular disease onset	17.861	17.490	18.232	18.044	17.677	18.412
Angina	19.697	18.997	20.396	20.183	19.476	20.891
Diabetes mortality	29.533	28.877	30.190	29.525	28.871	30.178
Stroke event	11.739	11.088	12.390	11.971	11.313	12.630
Event fatality	42.915	42.115	43.715	43.363	42.561	44.165
Myocardial infraction event	20.121	19.461	20.780	20.184	19.534	20.834

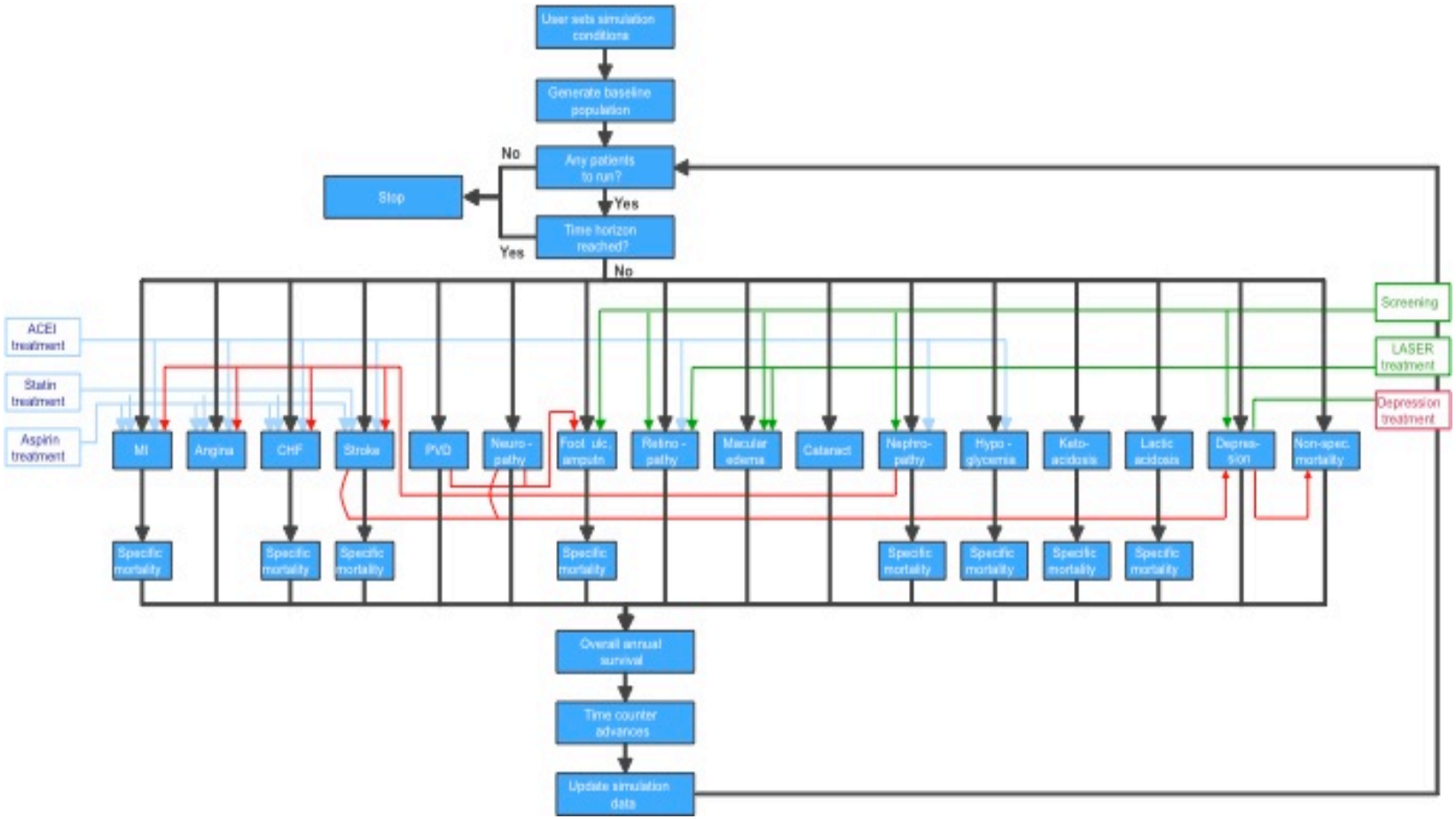
Supplement 13:

Table: Cumulative incidence eye disease

	GLP-1 (mean):	GLP-1 (CI low):	GLP-1 (CI high):	Placebo (mean):	Placebo (CI low):	Placebo (CI high):
BDR	29.729	29.277	30.180	29.240	28.810	29.670
PDR	1.596	1.556	1.636	1.560	1.521	1.598
ME	24.610	24.218	25.003	24.199	23.824	24.573
SVL	17.423	17.113	17.733	17.052	16.763	17.341
Cataract	12.640	12.446	12.834	12.445	12.259	12.632

Supplement 14:

Structural overview of the CORE Diabetes model including sub-models and their interactions:


User sets simulation conditions
Generate baseline population
Any patients to run?
No
Stop
Yes
Time horizon reached?
Yes
No
ACEI treatment
Statin treatment
Aspirin treatment
Screening
LASER treatment
Depression treatment
MI
Angina
CHF
Stroke
PVD
Neuro - pathy
Foot ulc, amputn
Retino - pathy
Macular edema
Cataract
Nephro - pathy
Hypo - glycemia
Keto - acidosis
Lactic acidosis
Depres - sion
Non-spec. mortality
Specific mortality
Overall annual survival
Time counter advances
Update simulation data

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