Journal of Medical Economics Vol. 15, No. 5, 2012, 977–986

1369-6998
doi:10.3111/13696998.2012.692340

Article 0015.R1/692340

Original article

Long-term cost-effectiveness of insulin detemir versus NPH insulin in type 2 diabetes in Sweden

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Key words:
Type 2 diabetes – Insulin detemir – Cost-effectiveness – Sweden

Accepted: 25 April 2012; published online: 23 May 2012
Citation: J Med Econ 2012; 15:977–86

Abstract

Aim:
To evaluate the cost-effectiveness of insulin detemir vs. NPH insulin once daily, in patients with type 2 diabetes in the Swedish setting based on clinical data from a published randomized controlled trial.

Methods:
Projections of long-term outcomes were made using the IMS CORE Diabetes Model (CDM), based on clinical data from a 26-week randomized controlled trial that compared once daily insulin detemir and NPH insulin, when used to intensify insulin treatment in 271 patients with type 2 diabetes and body mass index (BMI) 25–40 kg/m^2. Trial results showed that insulin detemir was associated with a significantly lower incidence of hypoglycemic events and significantly less weight gain in comparison with NPH insulin. The analysis was conducted from a third party payer perspective and the base case analysis was performed over a time horizon of 40 years and future costs and clinical outcomes were discounted at a rate of 3% per year.

Results:
Insulin detemir was associated with higher mean (SD) quality-adjusted life expectancy (5.42 [0.10] vs. 5.31 [0.10] quality-adjusted life years [QALYs]) and lower overall costs (SEK 378,539 [10,372] vs. SEK 384,216 [11,230]; EUR 33,794 and EUR 34,300, respectively, where 1 EUR = 11.2015 SEK) compared with NPH insulin. Sensitivity analysis showed that the principal driver of the benefits associated with insulin detemir was the lower rate of hypoglycemic events (major and minor events) vs. NPH insulin, suggesting that detemir might also be cost-saving over a shorter time horizon. Limitations of the analysis include the use of data from a trial outside Sweden in the Swedish setting.

Conclusions:
Based on clinical input data derived from a previously published randomized controlled trial, it is likely that in the Swedish setting insulin detemir would be cost-saving in comparison with NPH insulin for the treatment of patients with type 2 diabetes.

Introduction

In Sweden, the prevalence of type 2 diabetes is notably lower than in many other European countries and North America. Moreover, in contrast to a number of other European settings the incidence of type 2 diabetes in Sweden has remained relatively stable over the past few decades[1,2]. However, despite a relatively stable incidence the prevalence of type 2 diabetes has increased substantially in recent years. For example, in Uppsala, the prevalence of type 2 diabetes in adults aged ≥30 years increased from 3.8% to 5.7% over the period 1996–2003, representing an increase in prevalence of 6% per year[1]. This increase in prevalence has been largely attributed to declining mortality rates; with age- and sex-adjusted mortality rates in Uppsala, declining from 5.4 per 1000 to 4.1 per 1000 over the same period (1996–2003)[1]. It is feasible that the decline in mortality may be

attributable to advances in treatment, both in terms of the management of glycemic control and the primary and secondary prevention and treatment of a number of diabetes-related complications. The findings of a study by Eliasson *et al.*[3] concur with the suggestion that the management of patients with type 2 diabetes has improved in recent years. Over the period 1996–2003 mean HbA_{1c} decreased from 7.8% to 7.2% and mean blood pressure decreased from 150/82 mmHg to 143/78 mmHg. However, although these data suggest that risk factor control is improving, it should be noted that, over the same period, a substantial proportion of patients in Sweden did not reach targets for glycemic control, control of blood pressure and control of serum lipid levels[3].

Despite a relatively low prevalence and incidence of type 2 diabetes, the economic burden of type 2 diabetes in Sweden is still considerable. In 2005, it was estimated that diabetes and diabetes-related complications accounted for 1.4% of total healthcare spending in Sweden (in comparison with 1.0% in 1987)[4]. The substantial economic burden imposed by chronic conditions such as type 2 diabetes means that cost-effectiveness analyses of new (and established) interventions represent an important component in terms of assisting policy-makers and healthcare payers in decision-making and optimally allocating healthcare funding. Additionally, the economic burden associated with conditions such as type 2 diabetes is strongly influenced by disease stage, as such this must be taken into account when performing economic analysis. Patients with longer duration of disease generally have a higher prevalence of concomitant comorbidities and diabetes-related complications in comparison with those with less advanced disease, which has a notable influence on direct medical costs.

The PREDICTIVE BMI study was a 26-week randomized controlled trial in which 271 patients with type 2 diabetes (who had previously received twice daily insulin, with at least one dose being premix insulin) were randomized to receive either insulin detemir or NPH insulin once daily in the evening and insulin at main meals[5]. Insulin detemir is a long-acting insulin analog first approved in Europe in 2004 and which has been consistently associated with lower rates of hypoglycemic events in comparison with NPH insulin in randomized controlled trials[6]. In the PREDICTIVE BMI study basal insulin was titrated as required to achieve a pre-breakfast plasma glucose target of 6.1 mmol/L (without unacceptable hypoglycemia). At study end, HbA_{1c} had decreased from 8.9% at baseline to 7.8% in the insulin detemir group and from 8.8% to 7.8% in the NPH insulin group (the between-group difference was not statistically significant). However, the incidence of hypoglycemic events was significantly lower ($p < 0.0001$) in the insulin detemir arm in comparison with the insulin NPH arm. Mean body mass index (BMI) also increased over the study period in both treatment arms, but the magnitude of the increase in the insulin detemir arm was significantly lower than in the insulin NPH arm (+0.2 kg/m^2 in the insulin detemir arm vs. +0.6 kg/m^2 in the NPH insulin arm).

Previous cost-effectiveness analyses have examined the cost-effectiveness of insulin detemir vs. NPH insulin in patients with type 1 diabetes in Sweden and patients with type 2 diabetes in other settings such as Canada, Germany and the US. The Swedish analysis in patients with type 1 diabetes showed insulin detemir to be cost-effective compared with NPH insulin when considered from a healthcare payer perspective and dominant to NPH insulin when considered from a societal perspective. Similarly, in the Canadian setting insulin detemir was reported to be cost-effective vs. NPH insulin from a healthcare payer perspective. Notably, the lower rate of hypoglycemic events associated with insulin detemir was the key driver of results. Additionally, analyses in the German and US settings showed that conversion to insulin detemir ± oral antidiabetic agents from oral antidiabetic agents alone was either cost-effective or cost-saving[7,8]. To date the cost-effectiveness of insulin detemir vs. NPH insulin has not been investigated in patients with type 2 diabetes in the Swedish setting. As such the aim of the present analysis was to assess the long-term cost-effectiveness of insulin detemir vs. NPH insulin in patients with type 2 diabetes in Swedish based on clinical data from the PREDICTIVE BMI study[9,10].

Methods

Model

The cost-effectiveness analysis was performed using the IMS CORE Diabetes Model (CDM; IMS Health; Basel, Switzerland), which is a published and validated computer simulation model of type 2 diabetes. A brief overview of the CDM is provided here, but a more comprehensive description of the model structure and the validation analysis are available in the previously published articles by Palmer *et al.*[11,12]. In summary, the CDM is a non-product-specific policy analysis tool consisting of several interdependent semi-Markov models, which model the progression of diabetes-related complications. The individual sub-models use time, state and diabetes-type dependent transition probabilities to simulate the onset and progression of diabetes-related complications including: angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, ophthalmic complications, renal complications, hypoglycemia, ketoacidosis, lactic acidosis, foot ulcer and amputation. The use of tracker variables allows interaction between sub-models in cases where the onset of one complication influences the subsequent risk of development of another.

Each simulation models the progression of simulated cohorts of 1000 patients, which are run through the model 1000 times using first-order Monte Carlo methodology utilized to generate the mean and standard deviation estimates of life expectancy and quality-adjusted life expectancy as well as complication rates, time to onset of complications and direct and indirect medical costs.

Mean results from each iteration can then be utilized to create cost-effectiveness scatter plots, which can, in turn, be used to generate acceptability curves over a range of willingness-to-pay thresholds.

Simulation cohort and treatment effects

Baseline demographics and characteristics for the simulation cohort were derived from the PREDICTIVE BMI study and supplemented with data from Sweden-specific published sources where necessary (Table 1)[5,13–15]. Patients were predominantly Caucasian in terms of ethnicity, with a mean (SD) age of 61.9 (9.3) years and a mean duration of diabetes of 16.3 (8.7) years.

Treatment effects for the base case were derived from the PREDICTIVE BMI study. At 26 weeks, treatment with insulin detemir was associated with statistically significant benefits vs. insulin NPH in terms of both change in BMI and hypoglycemic event rate ($p<0.0001$ for both). However, the between-group difference in terms of HbA_{1c} reduction (measured using International Federation of Clinical Chemistry reference methods) was not statistically significant (Table 2). No treatment effect in terms of change from baseline in systolic blood pressure (SBP) or lipid levels was assumed (these data are not presented in the PREDICTIVE BMI study). Treatment effects for each arm were applied in the first year of the modeling simulation, after which risk factors (including HbA1c, lipid levels and blood pressure) in both arms followed a natural progression based on data from the United Kingdom Prospective Diabetes Study (UKPDS) and the Framingham Heart Study; BMI was assumed to remain constant throughout the simulation. Annual hypoglycemic events rates were assumed to remain unchanged throughout the simulation. For hypoglycemic events, major hypoglycemia was defined as an event that required third party assistance and minor hypoglycemia as an event that was self-managed.

Input data relating to the proportion of patients taking important concomitant medications that influence the risk of diabetes-related complications (i.e. aspirin, statins and angiotensin converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]) were derived from published literature specific to the Swedish setting[16–18]. For example, in the model patients taking aspirin have a projected reduction in risk of first and recurrent MI of 61% and 32%, respectively. Similarly, the use of statins and ACE inhibitors/ARBs have a considerable influence on MI incidence and/or outcomes.

Table 1. Simulated cohort characteristics.

Characteristic	Mean (SD)	Reference
Start age (years)	61.9 (9.3)	Fajardo-Montañana *et al.*[5]
Duration of diabetes (years)	16.3 (8.7)	Fajardo-Montañana *et al.*[5]
Percentage male (%)	40.6	Fajardo-Montañana *et al.*[5]
Percentage white (%)	99.3	Fajardo-Montañana *et al.*[5]
HbA_{1c} (%)	8.8 (1.0)	Fajardo-Montañana *et al.*[5]
SBP (mmHg)	150.1 (0)	Palmer *et al.*[14]
Total cholesterol (mg/dL)	187.6 (0)	Palmer *et al.*[14]
HDL-cholesterol (mg/dL)	49.8 (0)	Palmer *et al.*[14]
LDL-cholesterol (mg/dL)	103.5 (0)	Palmer *et al.*[14]
Triglycerides (mg/dL)	182.3 (0)	Palmer *et al.*[14]
Body mass index (kg/m^2)	31.8 (4.3)	Fajardo-Montañana *et al.*[5]

HbA_{1c}, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; SD, standard deviation.

Costs and utilities

Complication costs were derived from published literature[10,19–23]. All costs were expressed in 2010 Swedish Kronor (SEK) (Table 3), where necessary costs were inflated to 2010 values using consumer price index values sourced from the International Monetary Fund[24]. Pharmacy costs were calculated based on the basal and bolus insulin doses and oral anti-hyperglycemic agent (metformin) doses in the PREDICTIVE BMI study. Daily basal insulin doses were 0.59 IU/kg and 0.47 IU/kg in the insulin detemir and NPH insulin arms, respectively; daily bolus insulin doses were 0.46 IU/kg and 0.38 IU/kg, respectively. Costs for self-monitoring of blood glucose (SMBG) were also accounted for, based on data from a resource use study by Ringborg *et al.*[25], and the total annual treatment costs (including SMBG) were SEK

Table 2. Treatment effects from Fajardo-Montañana *et al.*[5] used in the base case analysis.

Effect	Detemir	NPH insulin	*p*-value for difference
Change from baseline in HbA_{1c} (%) (mean [SD])	−1.1 (1.1)	−1.0 (1.0)	Not significant
Change from baseline in BMI (kg/m^2)	0.2	0.8	<0.0001
Minor hypoglycemic event rate (events/100 patient years)	410	655	<0.0001
Major hypoglycemic event rate (events/100 patient years)	0	4	<0.0001

BMI, body mass index; HbA_{1c}, glycated haemoglobin

Table 3. Diabetes complication costs.

Complication	Cost (2010 SEK)	Reference
Cardiovascular and cerebrovascular complication costs		
MI (year of event)	90,597	Gerdtham *et al.*[19]
MI (years 2+)	2,126	Gerdtham *et al.*[19]
Angina (year of event)	107,438	Gerdtham *et al.*[19]
Angina (years 2+)	4,750	Gerdtham *et al.*[19]
CHF (year of event)	71,038	Gerdtham *et al.*[19]
CHF (years 2+)	6,720	Gerdtham *et al.*[19]
Stroke (year of event)	81,439	Gerdtham *et al.*[19]
Stroke (years 2+)	3,443	Gerdtham *et al.*[19]
Stroke death within 30 days	79,231	Gerdtham *et al.*[19]
PVD (year of event)	84,219	Gerdtham *et al.*[19]
PVD (years 2+)	4,687	
Renal complication costs		
Hemodialysis cost (year of event)[a]	532,012	Henriksson[20]
Annual cost of hemodialysis (years 2+)[a]	532,012	Henriksson[20]
Peritoneal dialysis cost (year of event)[a]	532,012	Henriksson[20]
Annual cost of peritoneal dialysis (years 2+)[a]	532,012	Henriksson[20]
Renal transplant cost (year of event)	291,646	Henriksson[20]
Annual cost of renal transplant (years 2+)	49,316	Henriksson[20]
Acute events		
Major hypoglycemic event[b]	29,082	Jönsson *et al.*[21]
Minor hypoglycemic event[b]	269	Jönsson *et al.*[21]
Ocular complication costs		
Laser treatment	6,793	Henriksson[20]
Cataract operation	16,633	Henriksson[20]
Blindness in year of onset	45,718	Schwarz *et al.*[22]
Blindness in subsequent years	1,233	Henriksson[20]
Neuropathy, foot ulcer and amputation costs		
Neuropathy (year of event)	41,589	Valentine *et al.*[10]
Amputation (event based)	148,753	Schwarz *et al.*[22]
Prosthesis (event based)	18,561	Ghatnekar *et al.*[23]
Gangrene treatment	23,942	Ghatnekar *et al.*[23]
Infected ulcer	16,012	Ghatnekar *et al.*[23]
Standard uninfected ulcer	13,933	Ghatnekar *et al.*[23]

CHF, congestive heart failure; MI; myocardial infarction; PVD, peripheral vascular disease.
[a]Assumed that dialysis costs are the same in year 1 and subsequent years.
[b]Cost of minor hypoglycemia assumes that a glucagon injection was administered, cost of major hypoglycemia assumes hospitalization was required and includes all direct medical costs associated with hospitalization.

14,922 per patient for insulin detemir and SEK 10,809 per patient for NPH insulin.

Health-related quality-of-life utilities were derived from the UKPDS and supplemented where necessary with utility values specific for patients with type 2 diabetes[26–31]. Of particular note a minor hypoglycemic event was associated with a disutility of −0.0033 and a major hypoglycemic event was associated with a disutility of −0.0118[30].

Discounting, time horizon and perspective

The base case analysis was performed from the perspective of a third party payer. In the base case analysis the time horizon was set to that of patient lifetimes (40 years) to capture all relevant long-term complications and associated costs, and to assess their impact on life expectancy and quality-adjusted life expectancy. Future costs and clinical benefits were discounted at a rate of 3% per year in line with published guidance for the Swedish setting[32].

Sensitivity analyses

A number of one-way sensitivity analyses were performed around key parameters and assumptions in the base case to assess the robustness of the analysis and to identify key drivers of outcomes. Sensitivity analyses were performed around the discount rate and time horizon, using time horizons of 5, 10, 15 and 20 years and changing the discount rate for both future costs and clinical outcomes to 0% per year and 6% per year. A sensitivity analysis was also performed in which the analysis was performed from a societal perspective (capturing both direct medical costs and indirect costs using the human capital approach). In addition to this, sensitivity analyses were performed around the cost of complications, where complication costs were increased

and decreased by 10% (treatment costs and indirect costs remained unchanged in these sensitivity analyses).

HbA_{1c} is known to be a key driver of long-term clinical outcomes in patients with type 2 diabetes. Consequently, a sensitivity analysis was performed in which the HbA_{1c} benefit associated with treatment with insulin detemir vs. NPH insulin was abolished (i.e. the change from baseline in HbA_{1c} was assumed to be the same as in the NPH insulin group). A further three sensitivity analyses were performed around the impact of hypoglycemic event rates on model outcomes. In the first analysis, hypoglycemic event rates (major and minor) were the only incremental treatment effects applied (HbA_{1c} reductions and changes in BMI were set to the same in both arms, with the values from the NPH insulin arm also applied to the insulin detemir arm). In the second analysis the benefit in hypoglycemic event rate in the detemir arm was abolished by setting the event rates (both major and minor) to the same as in the NPH insulin arm. In the third analysis the treatment cost associated with a minor hypoglycemic event was set to zero (the treatment cost associated with major hypoglycemic events remained unchanged).

The impact of the BMI benefit associated with insulin detemir was assessed in two separate sensitivity analyses. In the first sensitivity analysis, BMI was the only active incremental treatment effect (HbA_{1c} reductions and hypoglycemic event rates were set to the same in both treatment arms; values from the NPH insulin arm were applied in the insulin detemir arm). In the second BMI sensitivity analysis, the BMI benefit associated with insulin detemir was abolished by setting the increase in BMI in the detemir arm to the same as reported in the NPH insulin arm (HbA_{1c} and hypoglycemic event rates remained the same as in the base case). Additionally, in the base case no utility was associated with a change in BMI. Sensitivity analysis was performed in which lower BMI was associated with a quality-of-life benefit. The benefit was captured using one of two previously published quality-of-life utility scores from the Cost of Diabetes in Europe Type 2 (CODE-2) study, calculated using time trade off (TTO) and visual analog scale (VAS) quality-of-life instruments[31]. For patients in the insulin detemir arm, the applied disutilities were −0.0266 and −0.0203 for TTO and VAS, respectively, whilst for NPH insulin the respective disutilities were −0.0289 and −0.0220. These values were calculated from the BMI changes reported in the PREDICTIVE BMI study.

To investigate the impact of quality-adjusted life expectancy estimation methods on long-term cost-effectiveness, a sensitivity analysis was performed in which the quality-adjusted life expectancy estimation method used was a multiple regression formula from the University of Michigan, based on the self-administered quality of well-being (QWB-SA) instrument[33]. The final sensitivity analysis performed was around cohort characteristics. In the base case analysis cohort characteristics were derived from a combination of the Spanish cohort in the PREDICTIVE BMI trial and Swedish cohort data (Table 1). A sensitivity analysis was performed in which all baseline cohort characteristics were based on a previously published analysis in the Swedish setting[14]. Patients in this cohort had a similar age to patients in the base case (61.6 years vs. 61.9 years in the base case), duration of diabetes was 13.2 years (vs. 16.3 years in the basecase), mean HbA_{1c} was lower at 8.2% (vs. 8.8%) and systolic blood pressure was similar in both groups (150 mmHg in both cohorts).

Results

Base case analysis

In the base case analysis treatment with insulin detemir once daily was associated with improved mean (SD) life expectancy (8.69 [0.22] vs. 8.67 [0.16] years) and quality-adjusted life expectancy (5.42 [0.10] quality-adjusted life years [QALYs] vs. 5.31 [0.10] QALYs) in comparison with insulin NPH once daily. The benefit in life expectancy projected for the insulin detemir arm was attributable to a lower incidence of most diabetes-related complications, including ophthalmic complications, renal complications, ulcers and cardiovascular disease (Table 4). In addition to a lower cumulative incidence of complications, the mean time to onset of most complications was prolonged in the insulin detemir arm vs. NPH insulin. Patients in the insulin detemir arm remained complication-free for a mean of 0.93 years in comparison with 0.90 years in the insulin NPH arm.

Over a time horizon of 40 years, despite higher pharmacy costs (SEK 140,372 for insulin detemir vs. SEK 101,412 for NPH insulin) insulin detemir was associated with lower overall direct costs in comparison with NPH insulin due to complications avoided. The most notable difference in healthcare costs was in the total cost of hypoglycemic events (major and minor events; SEK 9959 for insulin detemir vs. SEK 52,266 for insulin NPH) (Table 4).

The mean values for the incremental benefits in direct costs and quality-adjusted life expectancy from the base case analysis were used to generate a cost-effectiveness acceptability curve and cost-effectiveness scatterplot (Figures 1 and 2, respectively). Analysis of the scatterplot shows that the data points are spread over three quadrants, but that the highest density of data points was in the lower right hand quadrant of the cost-effectiveness plane, indicating improved quality-adjusted life expectancy and lower costs for insulin detemir vs. NPH insulin. Consequently, the combination of improved life expectancy and improved quality-adjusted life expectancy

Table 4. Summary of results from base case analysis.

	Detemir	NPH insulin	Difference
Discounted life expectancy (years)	8.69 (0.15)	8.67 (0.16)	0.03 (0.22)
Quality-adjusted life expectancy (QALYs)	5.42 (0.10)	5.31 (0.10)	0.11 (0.14)
Lifetime direct medical costs (SEK)	378,539 (10,372)	384,216 (11,230)	−5,677 (15,365)
Treatment	140,372	101,412	38,960
Management	39,531	39,436	95
Cardiovascular disease	97,843	98,926	−1,083
Renal complications	29,660	30,423	−763
Ulcer/amputation/neuropathy	28,408	28,847	−439
Ophthalmic complications	32,766	32,906	−140
Hypoglycemic events (all types)	9959	52,266	−42,307
ICER based on life expectancy		Detemir dominant	
ICER based on quality-adjusted life expectancy		Detemir dominant	

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

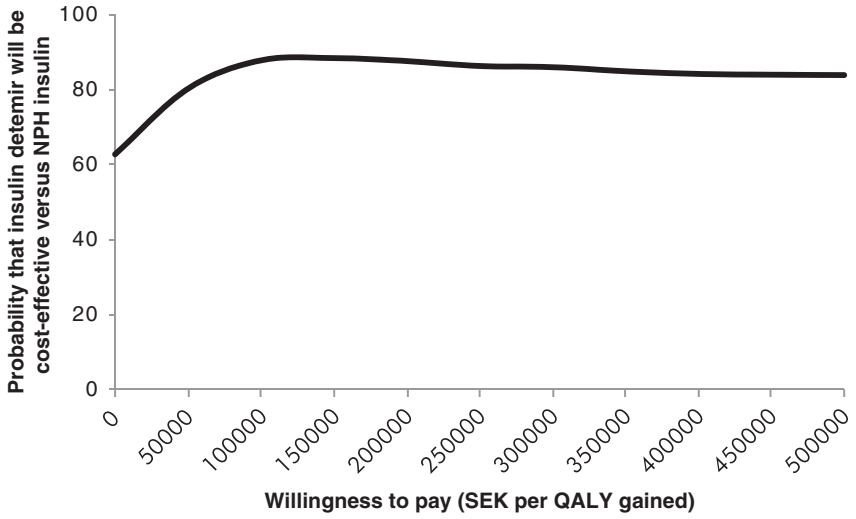

Figure 1. Cost-effectiveness acceptability curve.

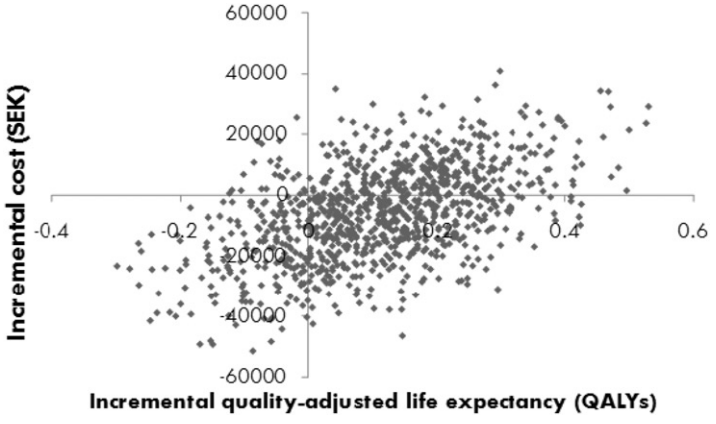

Figure 2. Cost-effectiveness scatterplot.

combined with lower direct costs suggest that if the results of the base case analysis are considered from the perspective of a third party payer, insulin detemir is dominant to NPH insulin in the Swedish setting.

Sensitivity analyses

One-way sensitivity analysis showed that the findings of the base case were robust and insensitive to changes in a number of parameters including changes in time horizon,

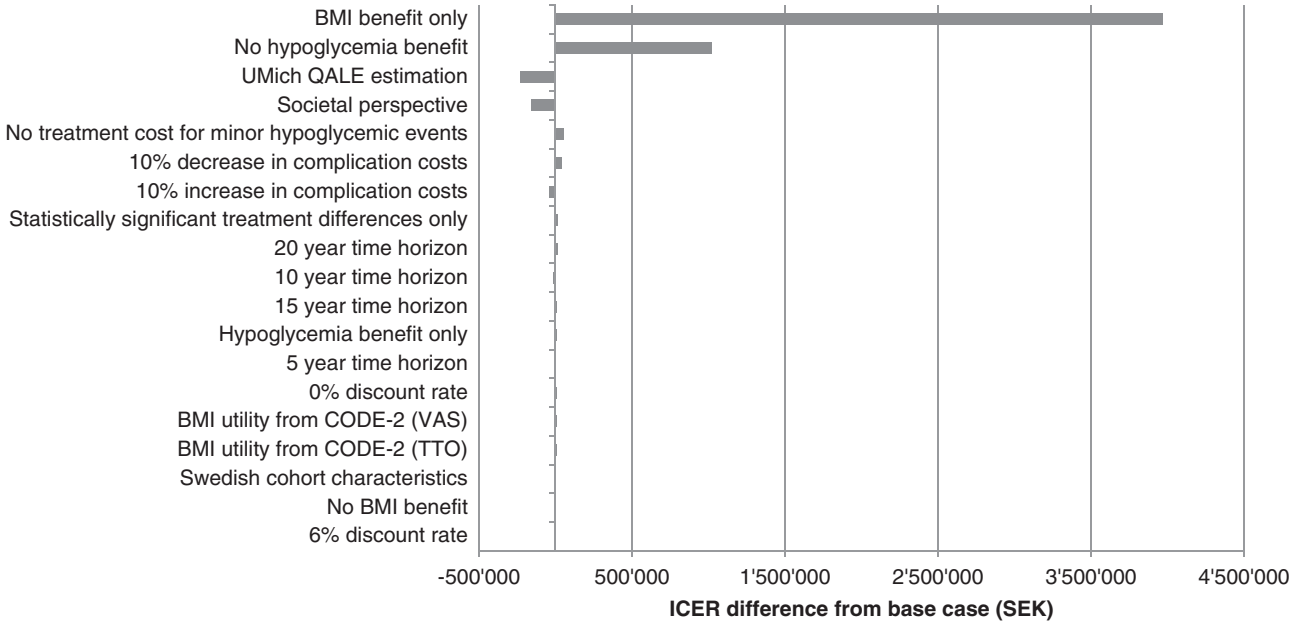

Figure 3. Sensitivity analysis: Tornado diagram: ICER difference from base case.

discount rate and cost of complications (Figure 3). If the results of the base case were considered from a societal perspective, insulin detemir remained dominant to NPH insulin with mean (SD) total (direct and indirect costs) being SEK 723,895 (20,111) for insulin detemir vs. SEK 747,112 (21,957) for NPH insulin. Sensitivity analyses also revealed that the lower rate of major and minor hypoglycemic events associated with insulin detemir in comparison with NPH insulin were a key driver of outcomes (minor hypoglycemic event rate was 410 events per 100 patient years for insulin detemir and 655 events per 100 patient years for NPH insulin; major hypoglycemic event rate was 0 per 100 patient years for insulin detemir vs. 4 per 100 patient years for NPH insulin). In the scenario in which the base case hypoglycemic event rate from the NPH insulin arm was applied to both treatment arms, the mean (SD) benefit in quality-adjusted life expectancy associated with insulin detemir was reduced to 0.04 (0.13) QALYs (vs. a benefit of 0.11 [0.14] QALYs in the base case). In this scenario, negating the benefit in terms of the lower incidence of hypoglycemic events associated with insulin detemir led to an incremental cost-effectiveness ratio (ICER) of SEK 995,590 for insulin detemir vs. NPH insulin. In the base case analysis it was assumed that treatment of a minor hypoglycemic event was associated with a cost of SEK 269, based on data from Jönsson *et al.*[21]. This was based on the assumption that a minor hypoglycemic event would require assistance from a second person (but would not require medical assistance) and involve a glucagon injection. However, it is likely that in many instances of minor hypoglycemic events a glucagon injection would not be required, as such a sensitivity analysis was performed in which the cost of a minor hypoglycemic event was reduced to zero. In this scenario insulin detemir was highly cost-effective, with an ICER of SEK 1356 per QALY gained vs. NPH insulin from a third party payer perspective (Table 5). If the results of this scenario were considered from a societal perspective, insulin detemir remained dominant.

In the PREDICTIVE BMI study, treatment with insulin detemir was associated with benefits in terms of BMI, hypoglycemic event rate and $HbA_{1c,}$ although the between-group difference in HbA_{1c} did not achieve statistical significance. Assuming that only the BMI benefit associated with insulin detemir was modeled (treatment effects in terms of HbA_{1c} and hypoglycemic event (major and minor) rates were set to that observed in the NPH insulin arm of the PREDICTIVE BMI in both arms of the simulation). Negating the HbA_{1c} benefit associated with insulin detemir, in addition to the benefit in terms of hypoglycemic event rates, thereby leaving lower BMI increase as the only clinical advantage, led to an ICER of in excess of SEK 3 million from a third party payer perspective. The results of this particular sensitivity analysis further demonstrate that the reduction in hypoglycemic event rates is a key driver of the cost-savings associated with the use of insulin detemir vs. NPH insulin once daily. Additionally, sensitivity analyses were performed in which only the BMI benefit associated with insulin detemir was modeled and in which different methods were used to estimate impact of changes in BMI on quality-adjusted life expectancy. In particular, quality-adjusted life expectancy remained slightly higher with insulin detemir vs. NPH insulin if only BMI benefit was modeled and the use of BMI utilities from the CODE-2 study (both time trade off and visual analog scale methods) increased the

Table 5. Summary of results from sensitivity analyses.

Analysis	Quality-adjusted life expectancy (QALYs)			Lifetime costs (SEK)			ICER (SEK per QALY gained)
	Detemir	NPH Insulin	Difference	Detemir	NPH insulin	Difference	
Base case	5.42 (0.10)	5.31 (0.10)	0.11 (0.14)	378,539 (10,372)	384,216 (11,230)	−5,677 (15,365)	Detemir dominant
One-way sensitivity analyses							
Societal perspective	5.42 (0.10)	5.31 (0.10)	0.11 (0.14)	723,895 (20,111)	747,112 (21,957)	−23,217 (19,475)	Detemir dominant
Time horizon							
5 year time horizon	2.61 (0.03)	2.56 (0.03)	0.04 (0.04)	145,756 (4,817)	148,263 (4,885)	−2,507 (6,938)	Detemir dominant
10 year time horizon	4.19 (0.06)	4.12 (0.06)	0.07 (0.09)	254,664 (7,316)	259,253 (7,798)	−4,589 (10,808)	Detemir dominant
15 year time horizon	4.97 (0.08)	4.86 (0.08)	0.11 (0.11)	323,630 (8,911)	327,991 (9,247)	−4,362 (12,929)	Detemir dominant
20 year time horizon	5.27 (0.10)	5.17 (0.09)	0.10 (0.13)	358,748 (10,119)	362,248 (10,056)	−3,500 (13,912)	Detemir dominant
Discount rate							
0% discount rate	6.79 (0.14)	6.64 (0.15)	0.15 (0.20)	498,514 (15,207)	505,051 (16,543)	−6,537 (22,752)	Detemir dominant
6% discount rate	4.47 (0.07)	4.38 (0.08)	0.09 (0.10)	299,761 (7,819)	304,683 (8,383)	−4,922 (11,474)	Detemir dominant
Complication costs							
10% decrease in complication costs	5.42 (0.10)	5.31 (0.10)	0.11 (0.14)	354,706 (9,458)	355,919 (10,213)	−1,213 (13,987)	Detemir dominant
10% increase in complication costs	5.42 (0.10)	5.31 (0.10)	0.11 (0.14)	402,355 (11,289)	412,496 (12,248)	−10,141 (16,746)	Detemir dominant
Treatment effects							
Statistically significant treatment differences only (BMI and hypoglycemia)	5.42 (0.10)	5.31 (0.10)	0.10 (0.14)	380,775 (10,882)	384,216 (11,230)	−3,441 (16,747)	Detemir dominant
BMI benefit only	5.32 (0.10)	5.31 (0.10)	0.01 (0.10)	423,380 (11,716)	384,216 (11,230)	39,165 (11,059)	3,012,692
Hypoglycemia benefit only	5.41 (0.10)	5.31 (0.10)	0.10 (0.14)	380,229 (10,998)	384,216 (11,230)	−3,986 (16,787)	Detemir dominant
No BMI benefit	5.41 (0.10)	5.31 (0.10)	0.10 (0.14)	378,507 (10,977)	384,216 (11,230)	−5,709 (16,235)	Detemir dominant
No hypoglycemia benefit	5.35 (0.10)	5.31 (0.10)	0.04 (0.13)	423,044 (11,317)	384,216 (11,230)	38,828 (14,178)	995,590
No treatment cost for minor hypoglyaemic events	5.44 (0.10)	5.31 (0.10)	0.11 (0.14)	368,579 (10,282)	368,429 (11,061)	151 (15,179)	1,356
Utility values							
BMI utility from CODE-2 (TTO)	5.17 (0.09)	5.04 (0.10)	0.13 (0.13)	378,539 (10,372)	384,216 (11,230)	−5,677 (15,365)	Detemir dominant
BMI utility from CODE-2 (VAS)	5.23 (0.10)	5.11 (0.10)	0.13 (0.14)	378,539 (10,372)	384,216 (11,230)	−5,677 (15,365)	Detemir dominant
UMich QALE estimation	4.59 (0.08)	4.57 (0.09)	0.02 (0.12)	378,539 (10,372)	384,216 (11,230)	−5,677 (15,365)	Detemir dominant
Cohort characteristics							
Swedish cohort characteristics (Palmer *et al.*[14])	6.01 (0.10)	5.90 (0.10)	0.11 (0.14)	391,860 (10,737)	396,863 (10,513)	−5,003 (14,827)	Detemir dominant

BMI, body mass index; TTO, time trade off; VAS, visual analog scale.

quality-adjusted life expectancy benefit to 0.13 QALYs (vs. 0.11 QALYs in the base case).

Discussion

In the PREDICTIVE BMI trial, insulin detemir was associated with benefits vs. NPH insulin in terms of HbA_{1c}, BMI and hypoglycemic event rates, although the benefit in terms of HbA_{1c} did not achieve statistical significance (it is also possible that the lower BMI gain in the insulin detemir arm may have had favorable implications in terms of SBP and lipid levels, but this remains speculative and as such was not included in the current analysis). The results of the present modeling analysis show that these benefits, particularly the lower hypoglycemic event rate associated with insulin detemir, were key drivers of the results of the cost-effectiveness analysis. The results of the base case analysis show that insulin detemir is likely to be dominant to NPH insulin; that is, associated with improved quality-adjusted life expectancy (and life expectancy) and lower costs from the perspective of a third party payer. Additionally, although the base case analysis was performed over a time horizon of 40 years, cost-savings with detemir were manifest over time horizons of as short as 5 years, suggesting that even in the short-term the clinical benefits of insulin detemir (in particular reduced hypoglycemic event rate) outweigh the slightly higher pharmacy cost in comparison with NPH insulin. An extensive series of one-way sensitivity analyses showed that the difference in hypoglycemic event rate was the principal driver of outcomes. In particular, in the base case analysis it was assumed, based on published literature, that the treatment cost associated with a minor hypoglycemic event was SEK 269, which was mostly attributable to the cost associated with a glucagon injection. However, many minor hypoglycemic events do not require this level of treatment, as such a sensitivity analysis was performed in which the cost of a minor hypoglycemic event was set to zero. In this scenario, insulin detemir was associated with an ICER of SEK 1356 per QALY gained vs. NPH insulin, which is likely to be considered highly cost-effective in the Swedish setting

The lower hypoglycemic event rate associated with insulin detemir reported in the PREDICTIVE BMI trial has been consistently reported across a number of randomized controlled trials comparing insulin detemir with NPH insulin. For example, in a pooled analysis of data from three phase III randomized controlled trials, Garber *et al.*[6] reported that the risk of hypoglycemic events (all types) was significantly lower in insulin detemir-treated vs. NPH insulin-treated patients aged 18–64 years (relative risk [95% CI] for detemir vs. NPH 0.75 [0.59–0.96]) and patients aged ≥65 years (relative risk [95% CI] for detemir vs. NPH 0.59 [0.42–0.83]). In the present analysis treatment effects were derived from the PREDICTIVE BMI study, which was conducted in the Spanish setting. However, given the consistency of the findings of studies comparing insulin detemir and NPH insulin, it is likely that if treatment effects had been sourced from the pooled analysis of Garber *et al.*[6], or the individual trials included in that analysis, the results of cost-effectiveness analyses would be comparable to those presented in the current analysis.

The fact that the clinical input data used in the analysis were derived from a study conducted in the Spanish setting is a limitation of the analysis, as it may limit the applicability of the findings to patients in the Swedish setting. However, patient management data were derived from published articles in the Swedish setting, thereby reflecting patient management practices in the Swedish setting. In recognition of this limitation, a sensitivity analysis was performed in which cohort characteristics were derived from a previously published cost-effectiveness study conducted in the Swedish setting using Swedish cohort data[14]. In this scenario, insulin detemir remained dominant to NPH insulin, although, notably, both life expectancy and quality-adjusted life expectancy were higher for both treatment arms in comparison with the base case (Table 5), which is likely attributable to differences between the two patient cohorts with regard to baseline characteristics and the prevalence of diabetes-related complications at baseline. Although the use of input data derived from the Spanish setting is a caveat of the current analysis, the results of sensitivity analyses have shown that the quality-of-life benefits associated with insulin detemir are largely driven by lower hypoglycemic event rates vs. NPH insulin. The results of a pooled analysis from three multinational studies shows that the lower hypoglycemic event rate has been consistently reported, suggesting that this is an effect that should be generalizable across settings. A second limitation of the present analysis is the reliance on short-term clinical data in making long-term predictions of outcomes over time horizons of up to 40 years. However, this is a limitation inherent to most cost-effectiveness modeling studies and, despite this, cost-effectiveness modeling studies, such as the one presented here, remain one of the best available options for making estimates of long-term clinical and economic outcomes in the absence of long-term clinical data.

In summary, the results of the present analysis suggest that in the Swedish setting insulin detemir once daily is likely to be associated with improved clinical outcomes and lower costs (both from a societal perspective and from the perspective of a third party payer) in comparison with NPH insulin once daily. As such the higher pharmacy costs associated with insulin detemir, in comparison with NPH insulin, should not represent a barrier to the use of insulin detemir in the Swedish setting.

Transparency

Declaration of funding
This study was funded by a grant from Novo Nordisk AB.

Declaration of financial/other relationships
JSP, RP and WV have disclosed that they are employees of Ossian Health Economics and Communications, which has received consultancy fees from Novo Nordisk AB to conduct this study. AE is an employee of Novo Nordisk.

Acknowledgments
The authors would like to acknowledge Barney Hunt from Ossian Health Economics and Communications for assistance in the preparation of figures used in the manuscript.

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