Advances in Therapy® | *Volume 23 No. 2*
March/April 2006

Cost-Effectiveness of Basal Insulin From a US Health System Perspective: Comparative Analyses of Detemir, Glargine, and NPH

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ABSTRACT

The purpose of this study was to compare in clinical and economic terms the long-acting insulin analogue detemir with intermediate-acting Neutral Protamine Hagedorn (NPH) insulin and with long-acting insulin glargine. Investigators used the validated Center for Outcomes Research (CORE) Diabetes Model to project clinical and cost outcomes over a 35-year base case time horizon; outcome data were extracted directly from randomized, controlled trials designed to compare detemir with NPH and with insulin glargine. Modeled patient characteristics were derived from corresponding trials, and simulations incorporated published quality-of-life utilities with cost data obtained from a Medicare perspective. Detemir, when compared with NPH, increased quality-adjusted life expectancy by 0.698 quality-adjusted life-years (QALYs). Lifetime direct medical costs were increased by $10,451 per patient, although indirect costs were reduced by $4688. On the basis of direct costs, the cost per QALY gained with detemir was $14,974. In comparison with glargine, detemir increased quality-adjusted life expectancy by 0.063 QALYs, reduced direct medical costs by $2072 per patient, and decreased

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indirect costs by $3103 (dominant). Reductions in diabetes-related comorbidities were also associated with detemir in both instances, most notably in the complications of retinopathy and nephropathy. Relative reductions in rates of complications were greatest in the comparison of detemir with NPH. Results were most sensitive to variation in hemoglobin A_{1c} (HbA_{1c}) levels. However, variation among any of the key assumptions, including HbA_{1c}, did not alter the relative results. Detemir represents an attractive clinical and economic intervention in the US health care setting compared with both NPH insulin and insulin glargine.

Keywords: type 1 diabetes; NPH; detemir; insulin glargine; modeling; costs; life expectancy; quality-adjusted life expectancy; cost-effectiveness

INTRODUCTION

The landmark Diabetes Control and Complications Trial (DCCT) of insulin treatment in type 1 diabetes clearly demonstrated that intensive insulin therapy administered over a 6.5-year period significantly reduces the incidence and progression of diabetic complications.[1] On the basis of the DCCT findings, current diabetes guidelines issued by the American Association of Clinical Endocrinologists recommend intensive insulin therapy for all patients with type 1 diabetes.[2] However, the DCCT also showed that intensive insulin therapy was associated with an increased incidence of hypoglycemia and weight gain.[3,4] The occurrence of hypoglycemia is largely due to the pharmacodynamics of commonly used human insulin preparations. Intermediate-acting insulins, such as Neutral Protamine Hagedorn (NPH) insulin, are characterized by a 12-hour duration of action that peaks approximately 5 hours after injection; patient absorption rates are highly variable.[5] Consequently, NPH must be injected twice daily by most patients, and it often fails to mimic physiologic insulin activity in that it begins more slowly, peaks later, and lasts longer than the endogenous insulin response. In an attempt to overcome these drawbacks, long-acting insulin analogues have recently been developed that exhibit a more rapid onset of action with a 24-hour duration and peak-less activity, resulting in a near-physiologic basal level of insulin between meals.[6] In numerous randomized clinical trials of long-acting insulin analogues, insulin detemir (IDet) and insulin glargine (IGlarg) have demonstrated at least equivalent or moderately improved glycemic control compared with NPH.[7-13] It is important to note, however, that treatment with IDet was associated with less weight gain, reduced within-patient variability, and decreased rates of nocturnal and major hypoglycemia when compared with NPH insulin.[7,9,10,14] The clinical efficacy and cost-effectiveness of IDet were recently highlighted in a combined clinical trial meta-analysis and economic cost-effectiveness evaluation of IDet versus NPH conducted in the United Kingdom.[15] On the basis of a meta-analysis of 4 relevant randomized studies, it was concluded that treatment with IDet (similar to IGlarg) results in modest improvements in glycemic control, reduced hypoglycemia, and less patient weight gain compared with NPH. In the long-term economic analysis, this translated into reduced complications and improved quality of life; these outcomes represent excellent value for money spent.[15] However, because of differences in health care and treatment costs between countries, investigators must evaluate the cost-effectiveness of treatments in a country-specific manner. For this reason, and on the basis of findings of a randomized, controlled trial

reported by Hermansen et al,[7] this report presents a discussion of the cost-effectiveness of IDet compared with that of NPH within the United States.

In a second and separate analysis that is presented in the following report, IDet is directly compared with IGlarg. This comparison has been made possible by the recent completion of a 26-week, multicenter, randomized trial of IDet and IGlarg administered in conjunction with the rapid-acting insulin aspart.[16] In this head-to-head comparison, it was found that although improvements in glycemic control were comparable, adverse events such as risk for major and nocturnal hypoglycemia were significantly less frequent with IDet treatment. The more predictable glucose-lowering effect of IDet compared with both NPH and IGlarg has been previously suggested on the basis of pharmacodynamic and pharmacokinetic studies conducted in patients with type 1 diabetes.[17] For the first time, it is now possible to directly compare these 2 long-acting insulin analogues from a clinical and an economic perspective on the basis of randomized clinical trial data.

In the following report, the validated Center for Outcomes Research (CORE) Diabetes Model is used to project the long-term clinical and economic benefits that might be anticipated with IDet treatment (either as a replacement for NPH or as an alternative to IGlarg) in the US health system setting. Because currently available clinical data for these new long-acting insulin analogues have been generated from trials of less than 12 months' duration, the use of a computer simulation modeling approach is one of the few ways by which long-term impact can be taken into consideration. By applying clinical trial results to simulation cohorts that closely resemble patients included in the trials, realistic assessments can be made in a defined cost setting. The following report represents a first attempt to predict the long-term clinical and economic potential of IDet in the US diabetes market.

METHODS

Two separate analyses were undertaken and are included in this report. The first analysis modeled the impact of IDet usage compared with NPH insulin. Data were extracted from an 18-week, open-label, randomized trial that compared treatment with twice-daily IDet given in conjunction with mealtime insulin (aspart) versus treatment with twice-daily NPH supplemented with human soluble insulin 30 minutes before meals.[7] In total, 598 patients with type 1 diabetes were randomized and monitored for changes in glycemic control, insulin dose, body weight, and adverse events. The latter cost-effectiveness analysis, reported here, compares the long-acting insulins IDet and IGlarg. Model projections have been based on results generated in a recently completed head-to-head, randomized trial of IDet and IGlarg, in which IDet was administered twice daily in combination with premeal insulin aspart (IAsp), and IGlarg was given once daily in combination with premeal IAsp.[16] Subjects were monitored over a 26-week period of treatment (6 weeks' titration and 20 weeks' maintenance); changes in glycosylated hemoglobin (HbA_{1c}) and body weight, hypoglycemic events, and other adverse events were recorded.

Model Description

Through the CORE Diabetes Model, the short-term clinical effects of IDet versus NPH and IDet versus IGlarg were simulated over a long-term horizon (35 years) from

the US health system perspective. The CORE Diabetes Model has been previously published in considerable detail.[18] Briefly, it is an interactive computer simulation model of diabetes that investigators developed for the purpose of determining the long-term health outcomes and economic consequences of interventions in type 1 or type 2 diabetes. Comprising 15 interdependent submodels, the model simulates the diabetic complications of angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy, end-stage renal disease, neuropathy, foot ulcer, amputation, and nonspecific mortality. Each submodel is a Markov model that uses time-, state-, and diabetes-type dependent probabilities derived from published sources; these are interconnected with the use of tracker variables. Patient cohorts can be defined in terms of age, sex, baseline risk factors, and preexisting complications, and disease management components can be altered in a disease management module. Similarly, economic data can be altered in an appropriate module that reflects the required setting. The CORE Diabetes Model thereby allows comparison of different patient populations in a variety of realistic clinical settings to yield long-term health and economic outcomes. Extensive validation of this model to ensure reliability of reported outcomes has been established in 66 separate analyses.[19]

Simulation Cohorts

Two separate simulation cohorts were defined according to the corresponding clinical trial from which clinical outcomes data were derived. Baseline characteristics of the 2 treatment arms within a given clinical trial were pooled to generate an appropriate simulation cohort; no statistical differences in baseline patient characteristics were noted between arms in either trial. The first cohort was based on a randomized, 18-week, multicenter clinical trial undertaken to compare IDet with NPH insulin in 595 patients with type 1 diabetes[7] (Table 1). The second cohort was modeled on the 26-week, randomized, multicenter clinical trial recently presented by Pieber et al.[16] In that trial, the long-acting insulin analogues IDet and IGlarg (both given in combination with rapid-acting insulin aspart) were compared in intensively treated subjects with type 1 diabetes (Table 1).

Treatment Effects

Treatment effects were extracted from the corresponding randomized clinical trials and were adjusted for baseline HbA_{1c}. The between–treatment group difference in HbA_{1c} was significant—a decrease of 0.5% versus 0.28%—with IDet versus NPH after 18 weeks, respectively.[7] The risk of hypoglycemia was 21% lower with IDet than with NPH ($P<.036$), and the risk of major hypoglycemia (defined as requiring third-party medical assistance) was nonsignificantly reduced at an event rate of 58 per 100 patient-years with IDet versus 66 per 100 patient-years with NPH. Nocturnal hypoglycemia and major nocturnal hypoglycemia, however, were significantly reduced in the IDet arm by 55% and 83%, respectively (both, $P<.008$). Furthermore, a significant difference in body weight was observed after 18 weeks of treatment; the adjusted weight change was 1 kg lower in the IDet treatment group than in the NPH group ($P<.001$).

Table 1. Baseline Demographics, Complications, Relevant Concomitant Medications, and Management of Patients in the Simulated Cohort

	Model Simulation Population IDet vs NPH	Model Simulation Population IDet vs IGlarg
Demographics		
Sex, % male	63	51.3
Ethnic origin, %		
Caucasian	99.8	95.3
Other	0.2	4.7
Mean age, y	39	40.2
BMI, kg/m^2	24.9	25.5
Mean duration of diabetes, y	15	17
Risk factors		
Glycosylated hemoglobin (HbA_{1c}), % points	8.38	8.84
Systolic blood pressure, mm Hg	124	127.9
Total cholesterol, mg/dL	208	208
High-density lipoprotein cholesterol, mg/dL	56.1	56.1
Low-density lipoprotein cholesterol, mg/dL	131.6	131.6
Triglycerides, mg/dL	97.4	97.4
Proportion smokers, %	20	19.6
Complications, %		
Left ventricular hypertrophy	1.2	0.5
Angina pectoris	0.5	2.4
Myocardial infarction	0	0.3
Heart failure	0.2	0.3
Atrial fibrillation	0.5	0.5
Stroke	0	0.4
Peripheral vascular disease	0	0.4
Neuropathy	0.3	1.5
Foot ulcer/amputation	0.2	0.2
Microalbuminuria	27.2	27.2
Gross proteinuria	9.6	9.6
Background diabetic retinopathy	42	24.0
Proliferative diabetic retinopathy	3.7	2.4
Severe vision loss	0.2	0.6
Cataract	1.7	2.8
Macular edema	9.2	9.2
Management, %		
Taking ACE-I/ARB	41.0	67.0
Taking statins	60.0	9.8
Taking aspirin	7.7	17.2
Screened for retinopathy (assumed treated with laser if detected)	48.2	75.0
Screened for renal disease (assumed treated with ACE or ARB if detected)	60	75.0
Proportion on foot ulcer prevention program	37.3	30.0

BMI=body mass index; ACE-I=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker.

In the randomized trial that compared IDet with IGlarg, HbA_{1c} decreased from 8.76% to 8.16% (–0.71% points) and from 8.70% to 8.19% (–0.62% points), respectively—a nonsignificant between–treatment group difference.[16] However, a significant reduction in major hypoglycemic events (72%) favored IDet; an event rate of 6.5 per 100 patient-years contrasted with a rate of 24.5 per 100 patient-years reported in the IGlarg treatment group ($P<.05$). Episodes of nocturnal hypoglycemia were also significantly reduced in the IDet arm (32% lower; $P<.05$). A nonsignificant difference in weight gain was also observed, although IDet was associated with a lower increase in body weight (0.52 kg) compared with the IGlarg group (0.96 kg). Although variation in the stability of glucose profiles was observed between arms in both trials, IDet-based treatment consistently exhibited reduced intra-day variability of fasting glucose levels compared with both NPH and IGlarg; these data were not included in the current analysis.

Costs

Cost analyses from a societal perspective within the US health care system were performed, and both direct and indirect costs were taken into account. Direct costs, which were regarded as the sum of treatment, complication, and medication costs as listed by Medicare, were inflated to 2005 values (as previously reported).[20] Indirect costs included those incurred through lost productivity; these were based on US-specific data on average salaries, retirement age, and days of work missed because of complications (data taken from the US Department of Labor, Bureau of Labor Statistics). All costs and clinical benefits were discounted at an annual rate of 3.0%, in accordance with recommendations for the US setting.[21] Acquisition costs of insulin were based on mean end-of-study dosing, and published Average Wholesale Price cost data (*2005 Drug Red Book;* Medical Economics Co., Inc., Montvale, NJ, USA) were used.

Quality-of-Life Utilities

Quality-of-life utilities were derived as previously described,[18] with the exception of utilities associated with hypoglycemic events. For major hypoglycemic events, an event disutility of –0.0121 quality-adjusted life-years (QALYs) was assumed on the basis of recently published data[22]; for all other hypoglycemic events, a value of –0.0052 QALYs was applied.[23] Event disutilities are applied in the model to the 1-year period in which the event occurred, as previously outlined by Palmer et al.[18] Subsequent state disutilities are applied for nontransient events that affect quality of life over a longer period.

Sensitivity Analysis

Sensitivity analysis was performed on key assumptions and variables used in the base case analysis: change in HbA_{1c}, discount rate, duration of treatment effect, and costs for insulin and management of hypoglycemia. The impact of changes in HbA_{1c} within the model was evaluated under 2 assumptions: (1) that improvements in HbA_{1c} were identical in the 2 treatment groups, and (2) that they persisted for only 5 years. Through assignment of a variable annual discount rate of between 0% and 6%, the impact of this variable on costs and clinical benefits was assessed relative to

the base case rate of 3.0% used in the simulation. Similarly, the time horizon was varied from the base case setting of 35 years to 5- and 10-year time horizons. Insulin detemir acquisition costs were varied by ±15% so that the impact of potential contractual rebate adjustments reflected within the US setting could be assessed; sensitivity to costs associated with major hypoglycemic events was assessed through application of the confidence intervals associated with the base cost as reported by Bullano et al.[24]

Statistical Approach

Analysis was performed by means of a nonparametric bootstrapping approach, in which the progression of diabetes was simulated in 1000 patients passed through the model 1000 times for calculation of the mean and standard deviations of life expectancy; quality-adjusted life expectancy and costs were derived through second-order Monte Carlo simulation.[25] A total of 1000 mean values (each of 1000 patients) for incremental costs and incremental effectiveness in terms of quality-adjusted life expectancy were plotted (scatter plots) on the cost-effectiveness plane, and these data were used to generate an acceptability curve through calculation of the proportion of points below a range of willingness-to-pay thresholds.

RESULTS

IDet versus NPH: Life Expectancy, Quality-Adjusted Life Expectancy, and Cost-Effectiveness

Long-term projections indicated that treatment with IDet compared with NPH was associated with improvements in life expectancy and quality-adjusted life expectancy (Table 2). Life expectancy (discounted by 3.0%) was improved by 0.168 QALYs with IDet compared with NPH insulin. Quality-adjusted life expectancy increased with IDet by 0.698 QALYs; average values consisted of 8.0 QALYs (±0.09) and 7.32 QALYs (±0.08) for IDet and NPH, respectively. Direct medical costs increased by $10,451 in the IDet treatment group relative to the NPH group; however, this was partially balanced by reduced indirect costs of $4688 to yield a total lifetime cost increase of $5763 among those using IDet. In the final cost-effectiveness analysis, treatment with IDet was associated with an incremental cost-effectiveness ratio (ICER) of $14,974 per QALY gained versus NPH on the basis of direct costs.

IDet versus NPH: Incremental Cost-Effectiveness Scatter Plot

In the base case analysis, most points in the incremental cost-effectiveness scatter plot (Fig 1) fell within the upper right quadrant, indicating that treatment with IDet was both more effective and more costly than NPH-based therapy. When this was converted to an acceptability curve, it could be seen that in the base case analysis, IDet-based treatment was associated with a 100% likelihood that it would be cost-effective versus NPH, if the willingness to pay was $50,000 per QALY gained.

Table 2. Summary of Base Case Results: IDet versus NPH

IDet vs NPH	IDet	NPH	Difference
Clinical outcomes, all settings			
Undiscounted life expectancy, y	21.346 (0.162)	21.026 (0.167)	
Discounted life expectancy, y	14.869 (0.162)	14.701 (0.167)	0.168
Quality-adjusted life expectancy, QALYs	8.018 (0.087)	7.32 (0.083)	0.698
Cost outcomes, US$			
Direct medical costs	118,746 (2805)	108,295 (2942)	+10,451
Indirect costs	141,809 (5034)	146,497 (5214)	–4688
Total lifetime costs	260,555 (7839)	254,792 (8156)	+5763
Outcome/ICER		14,974	

Values shown are means with standard deviations in parentheses. Values are expressed as means from 1000 cohorts, each of 1000 patients.

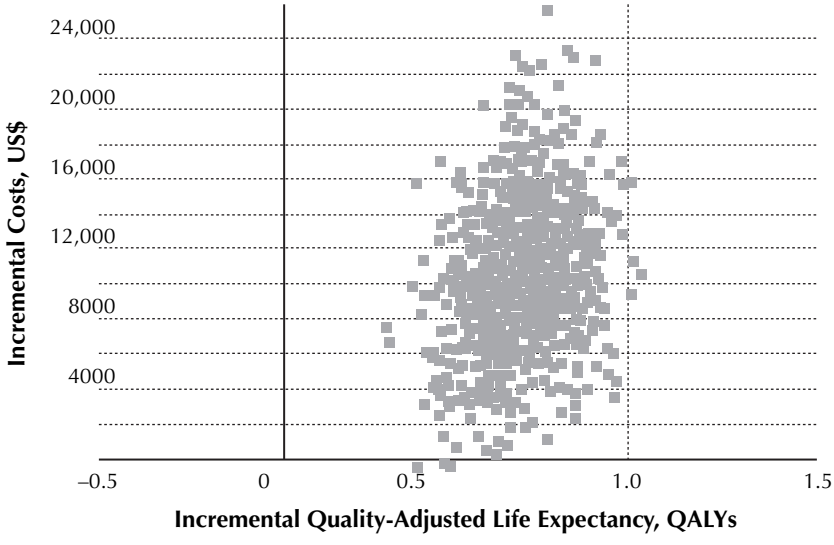
IDet versus NPH: Diabetes-Related Complications

Treatment with IDet compared with NPH resulted in an overall reduction in diabetes-related complications, most notably in retinopathy and nephropathy (Table 3). The greatest absolute reductions were projected for the cumulative incidences of proliferative diabetic retinopathy (PDR), end-stage renal disease (ESRD), microalbuminuria, and gross proteinuria, with values 0.8%, 0.8%, 2.1%, and 2.8% lower than those resulting from NPH treatment, respectively. Cardiovascular complication rates were generally similar between treatment groups, with the exception of myocardial infarction, for which the cumulative incidence was reduced by 0.7% with IDet compared with NPH.

Sensitivity Analysis

Sensitivity analysis revealed that the ICER for IDet versus NPH was most sensitive to changes in HbA_{1c}. However, even when no difference in efficacy with respect to HbA_{1c} was assumed between treatment groups, IDet was associated with an ICER of $20,386 per QALY gained versus NPH (Table 4). As would be expected, reducing the time horizon increased the ICER, because benefits that result from improvements in glycemic control tend to occur later rather than earlier. Nevertheless, variations in key assumptions (including price of IDet, discount rate, and cost of managing hypoglycemia) had no impact on the relative results and yielded ICERs below the $25,000 per QALY gained threshold used to define "attractive" diabetes interventions.[26]

Fig 1. Scatter plot and acceptability curve for IDet versus NPH. Base case scatter plot of 1000 samples of mean incremental costs plotted against mean incremental effectiveness (quality-adjusted life-years gained) generated for 1000 patients for IDet therapy versus NPH-based therapy.



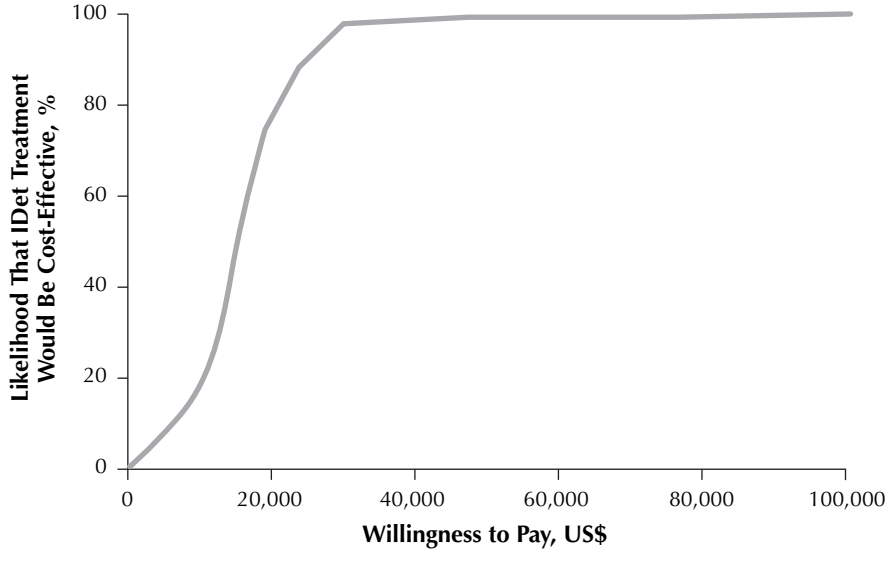


Table 3. Cumulative Incidence of Diabetes-Related Complications: IDet vs NPH and IDet vs IGlarg

Complication	Cumulative Incidence, % (SD)*			Cumulative Incidence, % (SD)*		
	IDet	NPH	Difference	IDet+IAsp	IGlarg+IAsp	Difference
Proliferative diabetic retinopathy	19.6 (1.2)	20.4 (1.3)	–0.8	18.13 (1.3)	18.93 (1.28)	–0.8
Severe vision loss	27.3 (1.4)	27.8 (1.4)	–0.5	23.9 (1.29)	23.6 (1.4)	+0.3
Microalbuminuria	67.0 (2.0)	69.1 (1.9)	–2.1	70.6 (1.8)	71.5 (1.8)	–0.9
Gross proteinuria	50.2 (1.8)	53.0 (1.7)	–2.8	53.4 (1.7)	54.7 (1.6)	–1.3
End-stage renal disease	19.2 (1.3)	20.0 (1.3)	–0.8	20.1 (1.3)	20.6 (1.3)	–0.5
First foot ulcer	49.3 (1.6)	49.6 (1.5)	–0.3	49.4 (1.5)	49.8 (1.6)	–0.4
First amputation due to an ulcer	14.9 (1.3)	15.2 (1.3)	–0.3	15.2 (1.3)	15.1 (1.4)	+0.1
Congestive heart failure	24.7 (1.3)	24.4 (1.3)	+0.3	27.4 (1.4)	27.2 (1.4)	+0.2
Myocardial infarction	36.0 (1.5)	36.7 (1.5)	–0.7	37.6 (1.5)	37.9 (1.5)	–0.3
Stroke	9.3 (0.9)	9.1 (0.9)	+0.2	9.0 (0.8)	9.1 (1.0)	–0.1

*Cumulative incidence of complications over patient lifetimes expressed as mean percentage (standard deviation) from 1000 cohorts, each of 1000 patients.

Table 4. Sensitivity Analysis on the Direct Incremental Costs per QALY

Assumption	Costs/QALY, $ IDet vs NPH	IDet vs IGlarg
Base case (assuming that HbA_{1c} improvements, decreased BMI, and decreased major hypoglycemia event rates occur simultaneously, 35-year horizon)	14,947	Dominant
5-year horizon	17,040	Dominant
10-year horizon	15,439	Dominant
Discount rate of 0%	14,910	Dominant
Discount rate of 6%	14,970	Dominant
Cost per major hypoglycemic event low	15,957	Dominant
Cost per major hypoglycemic event high	13,993	Dominant
IDet cost –15%	12,180	Dominant
IDet cost +15%	17,771	1126
No change in HbA_{1c}	20,386	Dominant
Change in HbA_{1c} lasts for only 5 years	16,781	Dominant

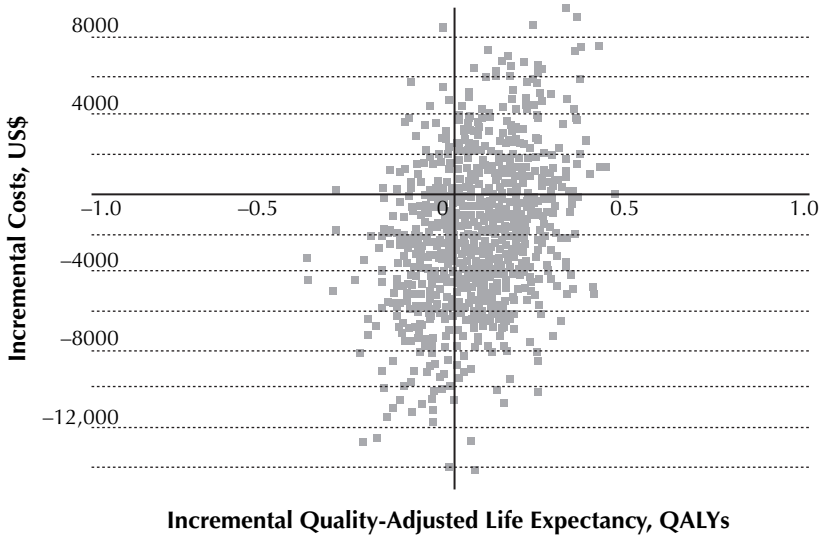
IDet versus IGlarg: Life Expectancy, Quality-Adjusted Life Expectancy, and Cost-Effectiveness

Treatment with IDet was associated with lower direct medical and indirect costs, as well as improved quality of life and life expectancy, when compared with treatment with IGlarg (Table 5). Discounted life expectancy was improved by 0.087 years and quality-adjusted life expectancy by 0.063 years with IDet. For IDet relative to IGlarg, direct medical costs were reduced by $2072 and indirect costs were reduced by $3103 per patient, resulting in overall lifetime cost savings of $5174 per patient from a societal perspective. In the cost-effectiveness analysis, IDet was therefore a dominant treatment option.

IDet versus IGlarg: Incremental Cost-Effectiveness Scatter Plot

In the base case analysis for IDet versus IGlarg, the incremental cost-effectiveness scatter plot (Fig 2) demonstrated that most points fell within the lower right quadrant, indicating that treatment with IDet was more effective and less costly than IGlarg-based therapy. However, there were a number of points in the upper right and lower left quadrants; when this plot was converted to an acceptability curve, it could be seen that in the base case analysis, IDet-based treatment had an 80% probability that it would be cost-effective, if the willingness to pay was $50,000 per QALY gained.

Fig 2. Scatter plot and acceptability curve for IDet versus IGlarg. Base case scatter plot of 1000 samples of mean incremental costs plotted against mean incremental effectiveness (quality-adjusted life-years gained) generated for 1000 patients for IDet therapy versus IGlarg-based therapy.



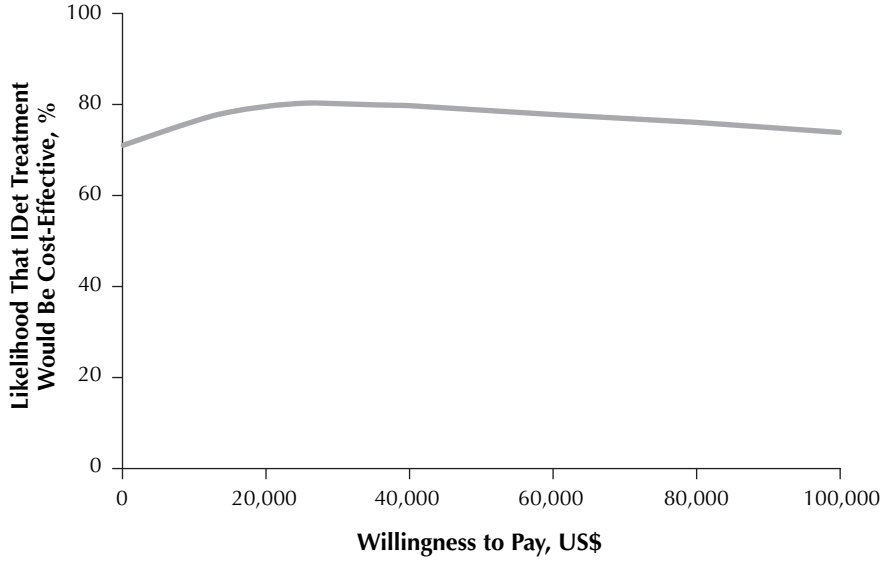


Table 5. Summary of Base Case Results: IDet vs IGlarg

IDet vs IGlarg	IDet + IAsp	IGlarg + IAsp	Difference
Clinical outcomes (all settings)			
Undiscounted life expectancy, y	20.12 (0.182)	19.958 (0.174)	
Discounted life expectancy, y	14.231 (0.182)	14.144 (0.174)	0.087
Quality-adjusted life expectancy, QALYs	7.242 (0.094)	7.179 (0.089)	0.063
Cost outcomes, US$			
Direct medical costs	108,208 (2768)	110,280 (2691)	2072
Indirect costs	144,145 (5456)	147,248 (5168)	3103
Total lifetime costs	252,354 (8225)	257,528 (7859)	5174
Outcome/ICER		Dominant	

Values shown are means with standard deviations in parentheses. Values are expressed as means from 1000 cohorts, each of 1000 patients.

IDet versus IGlarg: Diabetes-Related Complications

IDet treatment was associated with a reduced cumulative incidence of diabetes-related complications, particularly of retinopathy and nephropathy, when compared with IGlarg (Table 3). The corresponding absolute reductions in cumulative incidence of PDR, ESRD, microalbuminuria, and gross proteinuria were 0.8%, 0.5%, 0.9%, and 1.3%, respectively, for IDet versus IGlarg.

Sensitivity Analysis

When IDet was compared with IGlarg, results were most sensitive to changes in pharmacy acquisition costs, with an ICER of $1126 for a 15% increase in the cost of IDet. However, variation in the other key assumptions had no impact on relative results, and IDet remained dominant in the US setting (Table 1).

DISCUSSION

We have used the validated CORE Diabetes Model to analyze long-term economic and clinical outcomes that can be expected with uptake of the long-acting insulin detemir into the intensive treatment regimen of patients with type 1 diabetes within the United States. Compared with both intermediate-acting NPH insulin and an alternative long-acting insulin, IGlarg, model projections indicate that use of IDet is associated with improvements in life expectancy, quality-adjusted life expectancy, and cumulative incidence of diabetes-related complications. In economic terms, IDet represents a very attractive alternative to both NPH and IGlarg according to generally accepted standards.

Long-acting insulin analogues have been developed in response to high rates of major and minor hypoglycemia, both daytime and nocturnal, experienced by patients with diabetes who use NPH. The occurrence of hypoglycemia is a frequent complication

among intensively treated patients with type 1 diabetes; it affects overall patient quality of life and has the potential to be a life-threatening event.[27] Weight gain associated with insulin use is also a considerable problem for patients with diabetes. Apart from negative effects on blood pressure and lipid levels,[28,29] which exacerbate diabetic complications, increased weight often has an adverse effect on patient quality of life.[30] Randomized clinical trials comparing IGlarg with NPH have demonstrated improved or at least equivalent glycemic control, reduced incidence of hypoglycemia, and reduced weight gain with the former. Additionally, recent retrospective assessments of Medicaid claims in the United States reported that patients who used IGlarg, when compared with matched reference patients with diabetes, recorded lower event rates of hypoglycemia or greater reductions in event rates, as well as reduced treatment costs.[24,31] These early data suggest that the potential benefits exhibited by long-acting insulin analogues within controlled settings are already being realized in clinical practice. Before IDet was approved by the US Food and Drug Administration (FDA) in 2005, IGlarg was the only long-acting insulin analogue available in the United States. Preliminary trials directly comparing IDet and IGlarg for within-subject variability found that IDet had a significantly more predictable glucose-lowering effect than IGlarg, which, it was postulated, should result in fewer hypoglycemic events.[17] Indeed, a recently reported 26-week-long, head-to-head trial of IDet and IGlarg found a significant reduction in major hypoglycemic events associated with the use of IDet.[16]

To gain an appreciation for the long-term potential offered by IDet, we have used the CORE Diabetes Model to project over 35 years the short-term benefits observed with IDet versus NPH or IGlarg treatment in randomized clinical trials. Treatment with IDet has resulted in increased life expectancy, improved quality of life, and reduced complication rates compared with NPH; costs associated with these improvements are well within the limits of general acceptability at an ICER of $14,974 based on direct costs. According to Klonoff and Schwartz,[26] an ICER that is less than $25,000 should be considered a very attractive diabetes intervention.

In the comparison of IDet with IGlarg, although both are long-acting insulin analogues, IDet was shown to result in cost savings and an improved patient quality of life, making it a dominant option to IGlarg treatment. The between-group difference in complication event rates was, as anticipated, less than that seen for IDet versus NPH. Nevertheless, over a 35-year time projection, these differences translated into meaningful clinical and economic benefits favoring IDet.

Because long-acting insulin analogues offer relevant improvements and flexibility in diabetes care, both clinically and in terms of patient quality of life, interest in and uptake of these new insulins by clinicians are on the rise. For this reason, it becomes necessary to make timely clinical and economic decisions regarding their short- and long-term potential. Because the available trial data are based on relatively short periods of observation, use of appropriate and validated disease models to project long-term clinical and economic outcomes represents the best currently available approach by which clinicians can make evidence-based decisions on the basis of long-term assessments.

The present modeling study was based on randomized clinical studies conducted predominantly within European health care settings. Extrapolation of these findings to a US setting has permitted the prediction of likely economic and clinical outcomes in a US diabetes population. However, the necessity of confirming these short-term

clinical outcomes in a typical US diabetes cohort of representative ethnic diversity is acknowledged. With the recent completion (late in 2005) of a United States–based randomized trial of IDet versus IGlarg, new data can be used to further elucidate the relative merits of the conclusions presented here.

CONCLUSION

Among patients with insulin-dependent diabetes, basal bolus therapy with detemir was projected to yield improvements in life expectancy and quality-adjusted life expectancy when compared with either NPH or IGlarg. IDet was also associated with a reduced cumulative incidence of diabetes-related complications and consequently represents a clinically and economically attractive treatment option from a societal and reimbursement perspective in the US setting.

ACKNOWLEDGMENT

This study was supported by an unrestricted grant from Novo Nordisk Inc., Princeton, New Jersey, USA.

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