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Insulin therapy in type 2 diabetes patients failing oral agents: cost-effectiveness of biphasic insulin aspart 70/30 vs. insulin glargine in the US*

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Objectives: To project the long-term clinical and economic outcomes of treatment with biphasic insulin aspart 30 (BIAsp 70/30, 30% soluble and 70% protaminated insulin aspart) vs. insulin glargine in insulin-naïve type 2 diabetes patients failing to achieve glycemic control with oral antidiabetic agents alone (OADs).
Methods: Baseline patient characteristics and treatment effect data from the recent 'INITIATE' clinical trial served as input to a peer-reviewed, validated Markov/Monte-Carlo simulation model. INITIATE demonstrated improvements in HbA1c favouring BIAsp 70/30 vs. glargine (-0.43%; $p < 0.005$) and greater efficacy in reaching glycaemic targets among patients poorly controlled on OAD therapy. Effects on life expectancy (LE), quality-adjusted life expectancy (QALE), cumulative incidence of diabetes-related complications and direct medical costs (2004 USD) were projected over 35 years. Clinical outcomes and costs were discounted at a rate of 3.0% *per annum*. Sensitivity analyses were performed.
Results: Improvements in glycaemic control were projected to lead to gains in LE (0.19 ± 0.24 years) and QALE (0.19 ± 0.17 years) favouring BIAsp 70/30 vs. glargine. Treatment with BIAsp 70/30 was also associated with reductions in the cumulative incidences of diabetes-related complications, notably in renal and retinal conditions. The incremental cost-effectiveness ratio was \$46 533 per quality-adjusted life year gained with BIAsp 70/30 vs. glargine (for patients with baseline HbA1c $\geq 8.5\%$, it was \$34 916). Total lifetime costs were compared to efficacy rates in both arms as a ratio, which revealed that the lifetime cost per patient treated successfully to target HbA1c levels of $<7.0\%$ and $\leq 6.5\%$ were \$80 523 and \$93 242 lower with BIAsp 70/30 than with glargine, respectively.
Conclusions: Long-term treatment with BIAsp 70/30 was projected to be cost-effective for patients with type 2 diabetes insufficiently controlled on OADs alone compared to glargine. Treatment with BIAsp 70/30 was estimated to represent an appropriate investment of healthcare dollars in the management of type 2 diabetes.

Keywords: biphasic insulin aspart, cost-effectiveness, costs, INITIATE, insulin glargine, modelling, US
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Introduction

Studies have shown that due to declining beta-cell function in patients with type 2 diabetes, exogenous insulin treatment is usually required at some point as the disease progresses [1]. Patients commonly fail to attain sufficient glycaemic control solely with oral antidiabetic

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drugs, eventually requiring a switch to or the addition of exogenous insulin treatment. The initiation of insulin treatment typically includes either a premixed formulation of both basal and rapid-acting insulin such as insulin aspart or intermediate or long-acting basal insulin [2,3]. Premixed analogue insulins are thought to offer improvements in postprandial glucose levels and as a result are increasingly utilized over basal insulin alone due to the increasing recognition of the impact of postprandial glucose control on achieving overall glycemic targets [4–6].

The advantages of treatment with premixed insulin analogues over basal insulin alone have been demonstrated in a number of short-term studies [4,6,7]. Raskin et al. recently reported the findings of the INITIATE clinical trial which demonstrated that type 2 diabetes patients initiating insulin therapy with BIAsp 70/30 (70% insulin aspart crystallized with protamine and 30% soluble insulin aspart), achieved greater reductions in HbA1c and more frequently achieved target glycaemic levels than patients treated with insulin glargine [7]. A total of 66% of patients in the BIAsp 70/30 treatment arm reached the target HbA1c level of $<7\%$ vs. 40% of glargine-treated patients ($p < 0.002$), and 42% of BIAsp 70/30-treated patients reached $\leq 6.5\%$ vs. 20% of glargine-treated patients ($p = 0.0356$). Mean HbA1c levels were reduced by $-2.79 \pm 0.11\%$ in the BIAsp 70/30 group compared to $-2.36 \pm 0.11\%$ in the glargine group ($p = 0.0057$ between arms), however, patients with baseline HbA1C values $\geq 8.5\%$ (81% of all patients) experienced the most dramatic benefit of taking BIAsp 70/30 ($-3.13 \pm 1.63\%$ vs. $-2.60 \pm 1.50\%$, $p < 0.05$, BIAsp 70/30 vs. glargine, respectively). Mean body weight from baseline increased in both treatment groups, with a slightly greater weight gain observed in the BIAsp 70/30 treatment arm compared to the glargine group (5.4 ± 4.8 vs. 3.5 ± 4.5 kg, $p < 0.01$). Safety reports from the trial revealed that the overall rate of minor hypoglycaemia (plasma glucose < 56 mg/dl) was higher in the BIAsp 70/30 group (3.4 ± 6.6 episodes per patient year) than in the glargine group (0.7 ± 2.0 episodes per year). However, this did not seem to impede patients randomized to BIAsp 70/30 from reaching glycaemic targets. The only incident of a major hypoglycaemic episode was reported by a subject in the insulin glargine group.

When attempting to reduce the total cost burden of diabetes, healthcare payers need to identify cost-effective treatment interventions by comparing the value of available therapies among appropriate populations. Economic modelling is widely used together with short-term data from clinical trials to estimate the clinical and economic effects over long-term periods, not usually available from clinical trials. Results are typically expressed in life expectancy (LE) and quality adjusted life expectancy (QALE) and adds to policy and decision makers' decision base when prioritizing and allocating scarce healthcare dollars.

Numerous healthcare bodies within various international settings strongly recommend the inclusion of incremental cost-effectiveness analyses, expressed in terms of costs per life year gained or costs per quality-adjusted life year (QALY) gained, for payers to take into account during their reimbursement decision-making process. Most clinical studies are relatively short-term, collecting intermediate outcomes data, and are not long enough, large enough, nor designed to compare differences in LE or long-term costs. Economic modelling is an accepted tool used in outcomes research to estimate long-term clinical and cost consequences from data revealed by shorter-term trials.

The purpose of this study was to compare and project the long-term costs and clinical outcomes as an incremental cost-effectiveness analysis of treatment with BIAsp 70/30 vs. insulin glargine using results from a short-term clinical trial.

Methods

Model

The present analysis was performed using a non-product-specific, comprehensive and interactive computer-based Markov/Monte-Carlo model (CORE Diabetes Model) designed to calculate the long-term clinical and economic outcomes of treatment options and strategies in patients with either type 1 or type 2 diabetes. It has previously been described by Palmer et al. and has undergone extensive peer-review and validation [8,9]. Long-term outcomes are evaluated by tracking a user-specified group of patients through a series of sub models which simulate the progression of several diabetes-related complications [cardiovascular disease (CVD), eye disease, hypoglycaemia, nephropathy, neuropathy, foot ulcer, amputation, stroke, ketoacidosis, lactic acidosis and mortality]. Progression through these various Markov sub models are influenced by patient cohort characteristics which can include medical history, concomitant treatment medications, changes in physiological parameters which may occur over time, the frequency of screening for complications, and diabetes management strategy. Interaction between the sub models occur using tracker variables to overcome the 'memory-less' property associated with Markov models.

The model calculates the incidence of complications, costs, LE and QALE through the simulation of diabetes-related events in real time for a defined patient population. The reliability of the model's simulated outcomes has been tested and validated against the outcomes reported from published clinical and epidemiological trials [9].

Treatments and Simulation Cohort

In the INITIATE trial of 233 insulin naïve patients with type 2 diabetes, subjects previously unable to achieve glycaemic control on oral antidiabetic agents alone were randomly allocated to receive BIAsp 70/30 or insulin glargine. Before starting insulin therapy, metformin was optimized to 1000–2500 mg/day for a 4-week period, during which time secretagogoues and alpha-glucosidase inhibitors were discontinued. Patients taking any thaizolidinediones in both treatment arms were all administered pioglitazone before initiation of insulin therapy. In the BIAsp 70/30 treatment arm, patients with a fasting plasma glucose value <180 mg/dl were administered a total of 10 units daily while patients with a fasting plasma glucose values $\geq$ 180 mg/dl were administered a total of 12 units daily. Doses of BIAsp 70/30 were administered twice daily, before breakfast and an evening meal. Subjects randomly allocated to the glargine treatment arm were administered the entire dose at bedtime. Initial insulin dosage, adjusted weekly in the first 12 weeks and fortnightly thereafter, were titrated to achieve a target fasting plasma glucose and evening glucose values of 80–110 mg/dl.

The simulated population consisted of 1000 patients based on the characteristics of subjects in the INITIATE clinical trial. Baseline values comprised of 54.5% male with a mean baseline age of 52.45 years. On average, patients had been diagnosed with diabetes for 9 years with a mean HbA1c level of 9.77%-points [table 1]. Thirty-two per cent of patients in both treatment arms maintained the use of pioglitazone for the entire course of the simulation. Similarly, risk factors such as patients' history of complications, reported in the INITIATE study have been used and supplemented with additional data from published sources when required [7,10–13]. Within the simulation, patients were assumed to remain on the same treatment regimen for the entire length of the modelled disease progression (35 years or death).

Treatment Effects

Treatment effects observed in the INITIATE study were applied to the simulated cohort of patients within the model [table 2]. Improvements in HbA1c were observed in both treatment groups, with significantly greater reductions observed in the BIAsp 70/30 group. In the long term, progression of HbA1c levels in both treatment arms were assumed to gradually increase over time, in the same manner observed in the United Kingdom Prospective Diabetes Study (UKPDS) [14]. The initial increase in body mass index (BMI) observed in each of treatment group during the trial period was also accounted for in the model simulation. Subsequent changes in BMI used in the model were assumed to be similar to those observed in the NHANES II database. Insulin dosage at the beginning of the trial was similar for both groups, however, at the end of the study, insulin doses were significantly higher in the BIAsp 70/30

Table 1 Baseline demographics, complications, relevant concomitant medications, and management of patients in the simulated cohort

Characteristics	INITIATE study cohorts		Model simulation population
	BIAsp 70/30	Glargine	
Sex (%)			
Male	53.0	56.0	54.5
Female	47.0	44.0	45.5
Ethnic Origin (%)			
Caucasian	54.7	51.7	53.2
Hispanic	27.4	25.9	26.6
Black	14.5	17.2	15.9
Other	3.4	5.2	4.3
Age (years), mean (s.d.)	52.6 (10.6)	52.3 (9.8)	52.45
BMI (kg/m^2), mean (s.d.)	31.5 (5.5)	31.4 (5.3)	31.45
Duration of diabetes (years), mean (s.d.)	9.5 (5.9)	8.9 (4.8)	9
HbA1c (%), mean (s.d.)	9.70 (1.48)	9.84 (1.42)	9.77

Table 2 Summary of treatment effects based on the findings of the INITIATE study

	BIAsp 70/30	Glargine
Change from baseline in HbA1c (%-points)	−2.79	−2.36
Percentage of subjects reaching target HbA1c values (HbA1c < 7.0%)	65.7%	40.4%
Change from baseline in BMI (kg/m^2)	+1.88	+1.22
Increase from baseline to end of study in total dose of insulin (units per kg body weight)	+0.82	+0.55

group. As such, the observed increase in dosage and associated costs were applied to the simulation.

Costs

The economic evaluation included direct diabetes-specific costs of complications from the US which were inflated to 2004 values using a rate reported by the US Bureau of Labor and Statistics [table 3]. Evidence on the cost of treating diabetes complications suggests that the treatment may be more expensive for patients with diabetes than the general population, and as such, costs used in the present analysis were primarily collected from evaluations specifically estimating the costs of treating patients with diabetes [8,15–17]. The costs of the insulin and administration devices used in the INITIATE clinical trial were taken from US Pharmacy costs in 2004 [table 4].

Table 3 Cost per event or state used in the analysis, expressed in United States Dollars ($), 2004 values

Description of event or state	Annual costs ($)	Reference
Myocardial infarction, year of event	35 065	[16]
Myocardial infarction, each subsequent year	1938	[16]
Angina, year of onset	6957	[16]
Angina, each subsequent year	1797	[16]
Congestive heart failure, year of onset	3012	[16]
Congestive heart failure, each subsequent year	3012	[16]
Stroke, fatal	0	[16]
Stroke, year of event	46 435	[16]
Stroke, each subsequent year	15 497	[16]
Peripheral vascular disease, onset	4410	[32]
End-stage renal disease	42 763	[16]
Retinal photocoagulation	781	[16]
Severe vision loss/blindness, year of onset	3784	[16]
Severe vision loss/blindness, each subsequent year	3784	[16]
Cataract extraction	2488	[32]
Cataract annual follow-up	0	[16]
Neuropathy, onset	382	[16]
Uninfected ulcer	1658	[17]
Infected ulcer	2997	[17]
Gangrene	5847	[17]
Amputation, year of event	31 162	[16]
Amputation, prosthesis	1120	[16]
Major hypoglycemic event	257	[16]
Ketoacidosis	12 560	[16]
Annual cost aspirin	22	[33]
Annual cost statins	888	[33]
Annual costs ACE-I	399	[16]
Costs of screening for retinopathy	77	[16]
Costs of screening for nephropathy	17	[16]
Costs non-standard ulcer treatment	157	[34]

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.
Assuming one hospital admission at onset for investigation of symptoms.

Table 4 Cost of insulin and administration devices

	Year 1	Year 2+
NovoLog® Mix 70/30 10 ml	$1,891	$2,004
Lantus® 10 ml	$1,202	$1,249
Metformin (1500 mg)	$771	$771
Pioglitazone (30 mg)	$2,201	$2,201
Syringe	$97	$97

Prices in 2004 US Dollars.

Discounting, Time Horizon and Perspective

Economic and clinical outcomes were discounted at a rate of 3.0% *per annum* in the base case analysis in-line with recommendations from the US panel on cost-effectiveness in health [18]. The analysis was performed from the perspective of a third-party payer over a time horizon of 35 years. The chosen time horizon was assumed to be long enough to capture all relevant events and related complications associated with the progression of diabetes which occur throughout a patient's lifetime [19].

Sensitivity Analyses

The impact of varying the change in HbA1c, time horizon, discount rate, baseline age and the duration of treatment effects used in the base case analysis on the simulated outcomes was tested. The impact of changes in HbA1c on costs and QALE were evaluated under two different scenarios: [1] that improvements in HbA1c in the BIAsp 70/30 treatment arm were the same as observed in those treated with insulin glargine (−2.36%-points), and [2] that the improvement associated with BIAsp 70/30 over glargine was twice as large as that reported in the INITIATE study (BIAsp 70/30–3.22%-points).To investigate the impact of a shorter duration of treatment effect on HbA1c, a sensitivity analysis was performed assuming that the difference in HbA1c between the treatment arms persisted only for 2 years with HbA1c profile subsequently identical over the course of the simulation. The time horizon was varied between 0 and 35 years, with results reported at 5, 10 and 15 years in this paper. Variation in the time horizon provided data on the relative costs and clinical benefits for periods shorter than patients' lifetimes. The rates used to discount the projected clinical and economic outcomes were varied between 0 and 6% *per annum*. The baseline age in the simulated cohort was varied in two sensitivity analyses using higher baseline ages of 65 and 75 years to evaluate whether the relative costs and clinical benefits associated with each treatment option change with increasing age.

Statistical Approach

A non-parametric bootstrapping method, in which 1000 patients were simulated through the model 1000 times, was performed to calculate the mean and standard deviation in costs and QALE for both treatment options using second order Monte Carlo simulation [20]. Results for each of the 1000 iterations were used to create a scatterplot diagram comparing the incremental differences in costs and effectiveness for BIAsp 70/30 vs. insulin glargine. An acceptability curve was also generated based on the percentage of the sample means falling within a willingness to pay threshold between $0 and $50 000 from the scatterplot diagram.

Results

Base Case Analysis

Clinical Outcomes

Treatment with BIAsp 70/30 was projected to increase LE and QALE compared to insulin glargine in type 2 diabetes patients failing oral antidiabetic therapy [table 5]. In the simulated cohort, LE was projected to increase by 0.19 ± 0.24 years with BIAsp 70/30 (13.47 ± 0.17 years) compared to glargine (13.29 ± 0.16 years). The incorporation of quality of life values returned similar results, with an improvement of 0.19 ± 0.17 years in QALE with BIAsp 70/30 (9.40 ± 0.12 years) vs. glargine (9.21 ± 0.12 years).

Analysis of the cumulative incidence of diabetes-related complications showed notable reductions in the number of nephropathy and retinopathy complications over a patient's lifetime in those treated with BIAsp 70/30 compared to insulin glargine. For example, the cumulative incidence of end-stage renal disease was estimated to be 17% lower in patients treated with BIAsp 70/30 [8.6 ± 0.9%] when compared to glargine [10.3 ± 0.9%]. The cumulative incidence of severe vision loss, a complication resulting from the progression of diabetic retinopathy, was estimated to be 9% lower in patients treated with BIAsp 70/30 [26.2 ± 1.4%] compared to insulin glargine [28.8 ± 1.3%]. Differences in the cumulative incidence rates of other complications, such as cardiovascular events, were less pronounced [table 6].

Table 5 Summary of base case results

Characteristics	BIAsp 70/30	Glargine	Difference
Life expectancy (years)	13.47	13.29	+ 0.19
	(0.17)	(0.16)	(0.24)
Quality-adjusted life expectancy (QALYs)	9.40	9.21	+ 0.19
	(0.12)	(0.12)	(0.17)
Total lifetime costs	$107 393	$98 569	$8,824
	(2200)	(2227)	(3331)
ICER [based on quality-adjusted life expectancy] ($ per QALY gained)	–	–	$46,533

Values shown are means with standard deviation in parentheses. All values are rounded to two decimal places.

Lifetime Costs and Cost-effectiveness

The cost of treatment with BIAsp 70/30 over a patient's lifetime was estimated to be $8824 more expensive than insulin glargine (BIAsp 70/30 $107 393 ± 2200 vs. glargine $98 569 ± 2227). A breakdown of the lifetime costs revealed treatment costs for BIAsp 70/30 were $10 991 higher than insulin glargine, which is likely due to increased QALE in BIAsp 70/30. Nevertheless, the increase in per patient treatment costs with BIAsp 70/30 was partially offset by the reduction in the cost of treating diabetes-related complications, particularly a mean cost savings of $1236 in the treatment of nephropathy and $302 in the treatment of retinopathy compared to glargine therapy.

Based on these differences in lifetime costs and the improvements in QALE associated with BIAsp 70/30 treatment, the incremental cost-effectiveness ratio (ICER) for BIAsp 70/30 treatment vs. glargine was $46 533 per QALY gained. The mean incremental costs and QALE between BIAsp 70/30 and insulin glargine from 1000 bootstrap samples are displayed in a scatterplot diagram [figure 1]. The acceptability curve, which displays the probability of BIAsp 70/30 being cost effective given a particular willingness to pay, shows treatment with BIAsp 70/30 had a 60% probability of being cost effective compared to glargine assuming a willingness to pay threshold of $50 000 per QALY gained [figure 2].

Table 6 Cumulative incidence of diabetes-related complications

Complication	BIAsp 70/30	Glargine	Absolute Difference	Per cent difference
Retinopathy BDR	37.8 (1.6)	40.7 (1.6)	2.9 (0.0)	7% (0%)
Retinopathy PDR	4.3 (0.7)	5.0 (0.7)	0.7 (0.0)	14% (0%)
Severe vision loss	26.2 (1.4)	28.8 (1.3)	2.6 (−0.1)	9% (−8%)
Retinopathy ME	13.3 (1.0)	14.9 (1.1)	1.6 (0.1)	11% (9%)
Microalbuminuria	54.3 (1.6)	57.3 (1.6)	3.0 (0.0)	5% (0%)
Gross proteinuria	22.5 (1.3)	25.3 (1.3)	2.8 (0.0)	11% (0%)
End-stage renal disease	8.6 (0.9)	10.3 (0.9)	1.7 (0.0)	17% (0%)
Death from Nephropathy	3.6 (0.6)	4.5 (0.7)	0.9 (0.1)	20% (14%)
Ulcer, first	33 (1.4)	33.8 (1.6)	0.8 (0.2)	2% (13%)
Ulcer, reoccurrence	37.7 (3.1)	38.6 (3.3)	0.9 (0.2)	2% (6%)
First amputation due to an ulcer	8.9 (1.0)	8.9 (1.1)	0.0 (0.1)	0% (9%)
Neuropathy, onset	64.1 (1.7)	66.9 (1.6)	2.8 (−0.1)	4% (−6%)
Peripheral vascular disease, onset	22.9 (1.4)	24.5 (1.4)	1.6 (0.0)	7% (0%)
Congestive heart failure, first event	41.2 (1.6)	41.8 (1.6)	0.6 (0.0)	1% (0%)
Congestive heart failure, death	22.9 (1.3)	23.0 (1.3)	0.1 (0.0)	0% (0%)
Angina	25.9 (1.4)	25.6 (1.4)	−0.3 (0.0)	−1% (0%)
Myocardial Infarction, event	29.3 (1.5)	30.5 (1.5)	1.2 (0.0)	4% (0%)
Myocardial Infarction, death	19.4 (1.2)	20.1 (1.4)	0.7 (0.2)	3% (14%)
Stroke, event	15.6 (1.1)	15.3 (1.1)	−0.3 (0.0)	−2% (0%)
Death due to stroke	5.4 (0.7)	5.2 (0.7)	−0.2 (0.0)	−4% (0%)
Cataract	12.10 (1.0)	12.7 (1.1)	0.6 (0.1)	5% (9%)
Non-specific mortality	29.6 (1.4)	28.3 (1.5)	−1.3 (0.1)	−5% (7%)

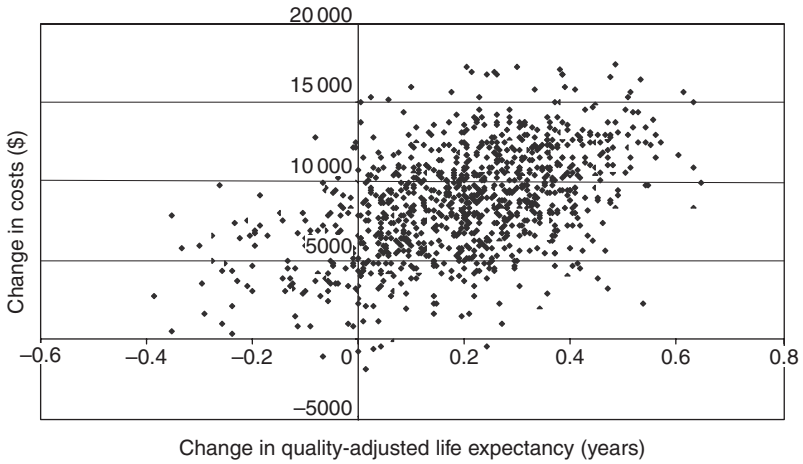

Fig. 1 Scatterplot of change in costs vs. change in quality-adjusted life expectancy for BIAsp 70/30 vs. glargine treatment.

Sub-Analysis of Cost-Effectiveness in Patients with Baseline HbA1c ≥ 8.5%

The INITIATE trial showed that patients with baseline HbA1c levels ≥ 8.5% had larger reductions in HbA1c than the total patient population. The reductions from baseline in HbA1c levels were 3.15 and 2.95% for BIAsp 70/30 and insulin glargine, respectively. Treating patients with high baseline HbA1c in an intensive manner may be particularly important in terms of reducing complication incidences and related costs. We therefore performed a sub-analysis in this cohort based on data from INITIATE (mean age 51.5 years; mean duration of diabetes 9 years; mean HbA1c: 10.2%) to evaluate long-term outcomes. The analysis showed that treatment with BIAsp 70/30 led to projected gains in incremental LE and QALE of 0.26 and 0.25 years, respectively, compared to glargine. Notable reductions in the cumulative incidence of retinal and renal complications were also projected (12% reduction in severe vision loss, 18% reduction in ESRD). Total lifetime costs were accounted to be $8908 more with BIAsp 70/30 than with glargine, leading to an ICER of $34 916 per QALY gained.

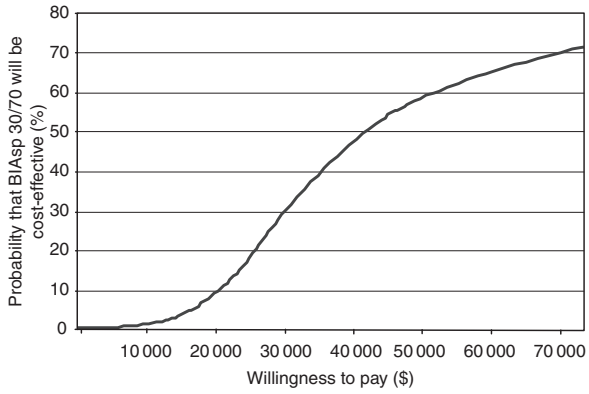

Fig. 2 Acceptability curve.

Costs of Treating Patients to Target HbA1c

We calculated the cost per patient treated to the target HbA1c level by dividing the average per patient costs by the percentage of patients reaching target HbA1c levels in each treatment group, assuming that the percentage of patients attaining the target HbA1c level (HbA1c < 7%) was similar over the lifetime horizon. Results showed that the cost per patient treated to the target HbA1c level (HbA1c < 7%) over the average patient's lifetime was estimated to be $80 523 lower in those treated with BIAsp 70/30 compared to insulin glargine ($163 460 vs. $243 983). When the number of patients in the INITIATE trial attaining a target HbA1c level below 6.5% was used, the difference in the average cost per patient treated to target increased to $93 242 (BIAsp 70/30 $257 537 vs. glargine $350 779).

Sensitivity Analyses

Sensitivity analysis performed on the change in HbA1c revealed that when the HbA1c values in the BIAsp 70/30 group were assumed to be the same as the glargine group (a reduction of 0.43%), glargine treatment was the dominant treatment choice (costs were lower by $10 335 and QALE was increased by 0.01 years) [table 7]. Varying the change in HbA1c in the opposite direction (mean HbA1c with BIAsp 70/30 set to 3.22%), BIAsp 70/30 resulted in an incremental gain in QALE of 0.42 years and increased costs by $7922, with ICER of $18 996 per QALY gained, compared to insulin glargine. Clinical and economic benefits were determined to be sensitive to the length of time at which a patient treated

Table 7 Sensitivity analyses

	QALE (QALYs)		Total Costs ($)		ICER (cost per QALY gained with BIAsp 70/30)
	BIAsp 70/30	Glargine	BIAsp 70/30	Glargine	
Base case analysis	9.40 (0.12)	9.21 (0.12)	$107 393 (2200)	$98 569 (2227)	$46,533
Variation of change in HbA1c					
Effect of BIAsp 70/30 reduced by 0.43%-points (same as glargine)	9.20 (0.12)	9.21 (0.12)	$108 904 (2410)	98 569 (2227)	Glargine dominant
Effect of BIAsp 70/30 increased by 0.43%-points above base case	9.63 (0.12)	9.21 (0.12)	$106 491 (2238)	$98 569 (2227)	$18,996$
Variation in duration of treatment effects					
HbA1c converges after 3 years	9.32 (0.12)	9.21 (0.12)	$108 505 (2299)	$98 569 (2227)	$91,316
Variation of time horizon					
Time horizon set to 5 years	3.29 (0.02)	3.28 (0.02)	$23 423 (480)	$20 317 (475)	$224,761
Time horizon set to 10 years	5.75 (0.05)	5.71 (0.05)	$45 596 (891)	$40 281 (951)	$123,032
Time horizon set to 15 years	7.45 (0.07)	7.36 (0.07)	$65 472 (1250)	$58 877 (1274)	$71,947
Variation of discount rates					
Discounting on costs and clinical benefits set to 0%	12.83 (0.20)	12.50 (0.18)	$165 247 (3929)	$152 679 (3908)	$38,564
Discounting on costs and clinical benefits set to 6%	7.25 (0.08)	7.13 (0.08)	$75 018 (1396)	$68 333 (1434)	$56,507
Variation of baseline age					
Baseline age set to 65	7.24 (0.11)	7.1 (0.10)	$86 568 (2139)	$79 088 (2074)	$53,668
Baseline age set to 75	5.48 (0.104)	5.3 (0.10)	$70 377 (2328)	$64 380 (2121)	$52,449

with BIAsp 70/30 maintained their reduction in glycaemic control. When the treatment effects of BIAsp 70/30 were assumed to last only 2 years, with HbA1c levels in BIAsp 70/30 equal to those in the glargine arm in subsequent years, treatment with BIAsp 70/30 improved QALE by 0.11 years compared to insulin glargine, with an ICER of $91 316 per QALY gained. Variation in the time horizon revealed that BIAsp 70/30 becomes better value for money compared to glargine as the time horizon is extended. The relative cost-effectiveness of treatment with BIAsp 70/30 compared to insulin glargine was sensitive to the different rates employed to discount costs and clinical benefits. Undiscounted, BIAsp 70/30 had an ICER of $38 564 per QALY gained and, discounted at 6% *per annum*, the ICER increased to $56 507 per QALY gained compared to insulin glargine. Further analyses using a higher baseline age demonstrated diminishing costs and benefits in both treatment arms. Assuming a baseline age of 65 and 75 years, with the same duration of diabetes as in the base case analysis of 9 years, treatment with BIAsp 70/30 had ICERs of $53 668 and $52 449 per QALY gained, respectively.

Discussion

Results from the INITIATE clinical trial, which reported improvements in HbA1c and an increased likelihood of attaining blood glucose targets in patients treated with BIAsp 70/30 compared to insulin glargine, were used to project the long-term clinical and economic benefits of such treatments among insulin naïve type 2 diabetes patients failing treatment with oral antidiabetic agents. The simulation projected increases in LE and QALE, as well as reductions in the cumulative incidence of diabetes-related complications such as nephropathy and retinopathy in the BIAsp 70/30 treatment arm compared to insulin glargine. Although BIAsp 70/30 treatment was projected to be more expensive over patient lifetimes, increased treatment costs were partially offset by a reduction in costly diabetes-related complications. The ICER for BIAsp 70/30 vs. glargine was $46 533 per QALY gained, falling below the threshold generally considered to represent good value for money in the US [21]. In a subgroup analysis of patients with baseline HbA1c $\geq$ 8.5%, the ICER for BIAsp 70/30 vs. glargine was estimated to be $34 916 per QALY gained. Sensitivity analysis revealed that the change from baseline in HbA1c was the main driver of long-term outcomes.

The sensitivity analysis performed under the assumption that the mean difference in HbA1c of 0.43% between BIAsp 70/30 and insulin glargine was only maintained for 2 years, with HbA1c profiles subsequently identical in both arms, increased the ICER to $91 316 per QALY gained. It seems unlikely that such a short-term effect on HbA1c would reflect the real-life

situation. Results from the UKPDS have shown that differences in glycaemic control in patients intensively treated compared to conventionally treated patients, were maintained over a 9-year period [22]. Our analysis revealed that the cost-effectiveness of BIAsp 70/30 is dependent upon sustained reductions in HbA1c which, as demonstrated in the base case analysis, resulted in a lower incidence of diabetes-related complications that partially offset higher treatment costs.

As the utilization of gains in LE and QALE data and their associated costs has increasingly become an outcome measure of importance to decision-makers, it is essential that such data are understood and interpreted appropriately and in the proper context. Gains in LE should be deemed meaningful only after thoroughly assessing the baseline characteristics and range of the measured population and the type of intervention being evaluated. For example, widely encouraged preventive interventions such as smoking cessation programmes or certain types of cancer screening evaluated across a public's health often yield very low gains in LE because reported gains are averaged across the entire population. As such, they may not provide information about the distribution of the gains actually realized by select patients. Therefore, a mean gain which seems small may represent a very large gain for a few patients who would have died prematurely without the intervention (a gain of a few days to a month may be enough to signal an important intervention). It is important to view LE as a variable applied to the shifting of a survival curve in a given population, not just simply the generic amount of life extension patients have tacked on because of a therapy.

Among populations with baseline characteristics similar to those in INITIATE, the added benefit of 0.20 years (approximately 3 months) exhibited in the BIAsp 70/30 arm vs. glargine compares favourably with other commonly adopted medical interventions. For example, 55-year-old men who have previously survived a myocardial infarction have been projected to have their survival curve shifted positively by 0.10–0.47 years when receiving routine beta-blocker therapy, and patients with advanced non-small cell lung cancer have been projected to a similar shift of 0.15–0.24 years when receiving chemotherapy.

Controlling HbA1c levels is the cornerstone of effective diabetes management [23]. Evidence of the benefits of stringent glycaemic control has been provided by large epidemiological and clinical studies which demonstrated that improvements in HbA1c levels reduced the incidence of complications associated with the progression of diabetes, including nephropathy, retinopathy, neuropathy and CVD [22,24–27]. For example, the UKPDS (33) reported that the risk of reaching any diabetes related end-point was 12% lower in patients intensively treated to attain a target HbA1c level of 7.0% compared to those conventionally treated to a target of 7.9% [22]. Comparable reductions in the risk of diabetes-related mortality, all-cause mortality, and developing microvascular complications were also reported. The importance of effective glycaemic control has been recognized in a number of international clinical practice guidelines. For instance, those published by the American Diabetes Association recommend a target HbA1c level of 7% for non-pregnant adults [23]. With these recommendations in mind, we calculated the cost of treating patients to target HbA1c over their lifetimes based on the efficacy rate findings of the INITIATE study. This sub-analysis provided evidence that BIAsp 70/30 is likely to be a more economically attractive treatment option than glargine when aiming to treat patients to a target HbA1c of 7% and $\leq$ 6.5%.

The present analysis used the clinical findings from a 28-week controlled trial to make long-term predictions about the clinical and economic value of premixed insulin aspart compared to long-acting insulin alone in type 2 diabetes patients. Although this approach may be viewed as a shortcoming, it is a criticism which could be applied to almost all modelling analyses. In the absence of long-term data, modelling based on the best available published data using validated methodology and done in a transparent fashion currently represents the best method of illustrating long-term clinical and cost outcomes. As healthcare budgets become increasingly limited, modelling has become a key tool to assess the long-term impact of different treatment options. To be accepted by clinicians and healthcare decision makers, the models used for these long-term projections must be transparent and corroborated against 'real life' data. The present evaluation was performed using the CORE Diabetes Model, which has previously been published and validated against the results from a number of published clinical and epidemiological studies [8,9].

The INITIATE study included patients with high HbA1c levels, a group generally considered to have poor compliance to treatment therapies. End of trial compliance rates revealed that more patients treated with BIAsp 70/30 requiring twice daily insulin injections discontinued treatment due to non-compliance with the trial protocol than those treated with once-daily glargine (4.2% vs. 2.5%). It appears plausible to assume that the compliance rate for BIAsp 70/30 would be lower than glargine in a real-life clinical setting due

to a higher frequency of insulin administration and as a result would inevitably impact long-term outcomes. However, it is interesting to note that patient satisfaction scores, evaluated using the Diabetes Treatment Satisfaction Questionnaire, revealed that patients treated with BIAsp 70/30 were more satisfied than those treated with insulin glargine (Novo Nordisk A/S, data on file).

A potential criticism of the present study is that the results from a short-term trial have been used to make long-term estimations about the economic and clinical benefits associated with each treatment option in the US population. The INITIATE study was a relatively small-scale trial, consisting of 233 patients, measuring the effects of each treatment option over a period of 6 months. The long-term efficacy of insulin analogues, such as BIAsp 70/30, has not been evaluated because of their new nature. Future clinical studies will be needed to shed light on this issue.

The results from the INITIATE trial, which was performed in a US population that included a relatively young cohort of patients with type 2 diabetes with a history of failing to achieve glycaemic control on oral antidiabetic medications, were used to make long-term estimations about the costs and effects associated with two treatment options in the present analysis. This clearly limits the generalizability of these results to other populations. However, it is noteworthy that the findings of INITIATE are supported by those of other trials, including long-term studies, measuring the efficacy of BIAsp 70/30 compared to biphasic regular human insulin in patients with type 2 diabetes [4,6,7,28,29]. In some of these trials, patients receiving BIAsp 70/30 achieved glycaemic control with a reduced number of hypoglycaemic events and reported higher amounts of patient satisfaction in follow-up questionnaires. Results from the INITIATE trial and another trials comparing biphasic insulin lispro 75/25 to treatment with insulin glargine, both combined with metformin, showed the greatest response to treatment in those with highest HbA1c levels (and possibly worse beta-cell function), suggesting that the patients with worse glycaemic control (HbA1c $\geq$ 8.5%) should be considered for biphasic insulin upon initiation of insulin treatment [30,31].

Conclusions

This health economic analysis suggests that long-term treatment with BIAsp 70/30 in insulin naïve type 2 diabetes patients failing oral antidiabetic therapy increases LE and QALE, as well as reduces the incidence of diabetes-related complications when compared to insulin glargine. Treatment with BIAsp 70/30 was estimated to represent an appropriate investment of healthcare dollars in the management of type 2 diabetes.

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