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ORIGINAL RESEARCH

Cost-Effectiveness of Biphasic Insulin Aspart versus Insulin Glargine in Patients with Type 2 Diabetes in China

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ABSTRACT

Background: The OnceMix and INITIATE studies have indicated that biphasic insulin aspart 30 (BIAsp 30) is more effective than insulin glargine (IGlarg), in terms of glycohemoglobin reductions, in patients with type 2 diabetes initiating insulin therapy. The cost-effectiveness of BIAsp 30 versus IGlarg in the Chinese setting is estimated here. ***Methods:*** The validated and peer-reviewed CORE Diabetes Model was used. The nephropathy, retinopathy, and stroke submodels were modified to incorporate available Chinese clinical data. Diabetes complication costs were derived from hospital surveys in Beijing and Chengdu. Simulated cohorts and insulin treatment effects were based on the OnceMix study for once-daily BIAsp 30 versus IGlarg and on the INITIATE study for twice-daily BIAsp 30 versus IGlarg. Life expectancy and direct medical costs were calculated. Projections were made over 30-year time horizons, with costs and life years discounted at 3% annually. Extensive sensitivity analyses were performed, including adjustments to cardiovascular risk for Chinese ethnicity. ***Results:*** Once-daily BIAsp 30 increased life expectancy by 0.04 years (12.37 vs. 12.33 years) and reduced direct medical costs by Chinese Yuan (CNY) 59,710 per patient (CNY 229,911 vs. CNY 289,621 per patient) compared with IGlarg in the OnceMix-based analysis. Twice-daily BIAsp 30 increased life expectancy by 0.08 years (12.99 vs. 12.91 years) and reduced direct medical costs by CNY 107,349 per patient (CNY 303,142 vs. CNY 410,491 per patient) compared with IGlarg in the INITIATE-based analysis. Improvements in life expectancy were driven by reduced incidences of most diabetes-related complications. Cost savings were attributable to lower lifetime insulin costs for BIAsp 30 compared with IGlarg in China. Lowered cardiovascular risk for Chinese ethnicity reduced the projected clinical improvements for BIAsp 30 but increased treatment-related lifetime cost savings. ***Conclusions:*** BIAsp 30, either once- or twice-daily, improved projected life expectancy and reduced projected costs compared with IGlarg in the Chinese setting.

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INTRODUCTION

Diabetes mellitus is an increasing problem in middle-income countries, where patient numbers are rising. According to recent estimates the number of patients with diabetes in China is expected to increase from 20.8 million in 2000 to 42.3 million by 2030.[1] The reasons for the projected increase are manifold, but may include continued urbanization,[2] changing nutritional patterns,[3] and decreasing mortality from communicable diseases.[4]

Diabetes is associated with substantial medical costs in China due to the high cost of its complications.[5-7] It is likely that more resources are directed at treating the costly complications of diabetes rather than preventing their occurrence. This is the pattern observed in European countries, where hospitalization costs represent the largest share of overall expenditure in patients with diabetes.[8] Additionally, out-of-pocket costs represent a large share of medical expenditure in China,[9] and pharmaceutical spending, most of which is out-of-pocket, accounts for roughly half of total healthcare expenditure.[10] There is a compelling need to identify effective and economical treatments for patients with diabetes in China.

In type 2 diabetes, patients typically commence therapy with one or two oral antidiabetic agents (OADs), such as metformin or a sulfonylurea, to improve insulin sensitivity and secretion. Based on observations of the United Kingdom Prospective Diabetes Study (UKPDS), progressive decline in beta-cell function leads to decreased endogenous insulin production over time, necessitating the initiation of insulin therapy.[11,12] Recent clinical trials have been performed in insulin-naïve patients experiencing poor glycemic control on OADs. In the INITIATE study, twice-daily biphasic insulin aspart 30 (BIAsp 30) reduced glycohemoglobin (HbA_{1c}) significantly more than insulin glargine (IGlarg),[13] and in the OnceMix study, once-daily BIAsp 30 reduced HbA_{1c} significantly more than IGlarg.[14] In both randomized clinical trials BIAsp 30 was associated with greater weight gain, higher insulin dosage, and more frequent hypoglycemia than IGlarg. The aim of the current analysis was to estimate the long-term cost-effectiveness of once-daily BIAsp 30 versus IGlarg based on the OnceMix study and twice-daily BIAsp 30 versus IGlarg based on the INITIATE study for insulin-naïve patients with type 2 diabetes in China.

MATERIALS AND METHODS

Model

The CORE Diabetes Model was used for the cost-effectiveness analyses.[15] The model is a nonproduct-specific, diabetes policy analysis tool that performs real-time simulations taking into account intensive or conventional insulin therapy, concomitant OADs and lipid-lowering therapies, aspirin and angiotensin-converting enzyme inhibitor (ACEI) usage, and screening and treatment strategies for microvascular complications and end-stage complications. Disease progression is based on a series of interdependent Markov submodels that simulate diabetes-related complications (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macular edema, cataract, hypoglycemia, ketoacidosis, nephropathy and end-stage renal disease [ESRD], neuropathy, foot ulcer, and amputation). Each submodel uses time-, state-, and diabetes type-dependent

probabilities derived from published sources, utilizing tracker variables to overcome the memory-less properties of standard Markov models. Analyses, including first- and second-order Monte Carlo simulations, can be performed on patient cohorts with type 1 or type 2 diabetes, defined in terms of age, gender, baseline risk factors, and pre-existing complications. The simulation of relevant physiological parameters (such as HbA_{1c} and systolic blood pressure) is based on long-term epidemiological data, and influence event risks. The model is adaptable, allowing the inclusion of new data as it becomes available. The reliability of simulated outcomes has been tested, with results validated against those reported by clinical trials and epidemiological studies.[16]

China-specific clinical data were incorporated in the present modeling analysis. Life table data from the World Health Organization (WHO) were used for the calculation of nonspecific mortality[17] and were adjusted for modeled causes of death based on WHO Global Burden of Disease estimates.[18] Transition probabilities for ESRD treatment modalities (hemodialysis, peritoneal dialysis, or renal transplant) and subsequent survival were also incorporated and were China-specific.[19,20] The increased risk of cardiovascular events for patients with microalbuminuria and gross proteinuria was captured, based on the analysis of 4416 patients with type 2 diabetes followed up for a median of 41 months at the Chinese University of Hong Kong.[21] Event rates simulating the onset and progression of diabetic retinopathy were derived from a Hong Kong-based study, where 413 patients with type 2 diabetes were followed up for 4 years.[22] Retinopathy risks were modified according to the HbA_{1c} level of the simulated patient, based on data from the UKPDS.[23] Data from the China Multicenter Collaborative Study of Cardiovascular Epidemiology were also incorporated; a 28-day stroke case fatality rate of 35% was reported in a mixed urban and rural population,[24] and was applied in the stroke submodel.

Simulated Cohorts

Cohorts of patients with type 2 diabetes for simulation in the model were defined based on the OnceMix and INITIATE studies (Table 1). The model requires a range of patient demographic, physiological parameter, and baseline comorbidity data in order to make long-term clinical projections. Therefore, where necessary information from the OnceMix and INITIATE studies were unavailable, data were derived from a previously published modeling analysis of patients with type 2 diabetes using insulin in China,[5] supplemented with tobacco and alcohol consumption data from the WHO.[25,26]

Treatment Effects

Reductions in HbA_{1c} for the initiation of insulin therapy were based on data from the OnceMix and INITIATE studies (Table 2). Subsequent changes in HbA_{1c} for each simulated patient were based on published equations from the UKPDS Outcomes Model.[27] Initial increases in body mass index (BMI) were based on OnceMix and INITIATE data; no subsequent changes in BMI were modeled in the simulations. Major and minor hypoglycemia were captured in the modeling analysis, based on the extrapolation of event rates reported in the respective clinical studies. All available treatment-effect data from OnceMix and INITIATE were applied in the simulations, even if the between-treatment differences were not statistically significant.[28]

Table 1. Simulated cohorts based on OnceMix and INITIATE studies.

	BIAsp 30 q.d. vs. IGlarg q.d. (OnceMix cohort)	BIAsp 30 b.i.d. vs. IGlarg q.d. (INITIATE cohort)
Patient demographics		
Baseline age, years	56.00	52.45
Duration of diabetes, years	9.30	9.20
Proportion male, %	43.90	54.50
Baseline risk factors		
HbA_{1c}, % points	9.00	9.75
Systolic blood pressure, mmHg	130.40	137.70
Total cholesterol, mg/dL	184.61	207.30
High-density lipoprotein cholesterol, mg/dL	46.15	50.30
Low-density lipoprotein cholesterol, mg/dL	103.84	143.80
Triglycerides, mg/dL	200.00	219.50
BMI, kg/m^2	29.10	31.45
Proportion smokers, %	36.00	36.00
Cigarettes per day	14.00	14.00
Alcohol consumption, Oz/week	2.86	2.86
Racial characteristics, %		
Proportion Asian/Pacific Islander	100	100
Baseline CVD complications, %		
Proportion with myocardial infarction	0.0	2.2
Proportion with angina	0.0	1.7
Proportion with peripheral vascular disease	5.5	0.9
Proportion with stroke	0.0	0.0
Proportion with congestive heart failure	0.0	0.4
Proportion with atrial fibrillation	5.5	1.3
Proportion with left ventricular hypertrophy	0.0	0.0
Baseline renal complications, %		
Proportion with microalbuminuria*	5.5	4.0
Proportion with gross proteinuria	0.0	4.0
Proportion with end-stage renal disease	0.0	0.0
Baseline eye complications, %		
Proportion with background retinopathy	20.5	8.5
Proportion with proliferative retinopathy	0.0	0.0
Proportion with macular edema	0.0	0.0
Proportion with severe vision loss	0.0	0.0
Proportion with cataract	0.0	4.3
Baseline neuropathy, %		
Proportion with neuropathy	22.6	23.2

BIAsp 30=biphasic insulin aspart 30; b.i.d.=twice a day; BMI=body mass index; CVD=cardiovascular disease; HbA_{1c}=glycohemoglobin; IGlarg=insulin glargine; Oz=fluid ounces; q.d.=once a day.
*One-way sensitivity analysis performed for this input.

Table 2. Summary of treatment effects and hypoglycemia data based on the OnceMix and INITIATE studies.

OnceMix	BIAsp 30 q.d.	IGlarg q.d.
Change from baseline in HbA_{1c}, % points	–1.41	–1.25
Change from baseline in BMI, kg/m^2*	0.72	0.68
Major hypoglycemia (events per 100 patient-years)*	2.72	2.63
Minor hypoglycemia (events per 100 patient-years)	650.00	480.00
INITIATE	**BIAsp 30 b.i.d.**	**IGlarg q.d.**
Change from baseline in HbA_{1c}, % points	–2.79	–2.36
Change from baseline in BMI, kg/m^2	1.88	1.22
Major hypoglycemia (events per 100 patient-years)*	0.00	1.61
Minor hypoglycemia (events per 100 patient-years)	340.00	70.00

BIAsp 30=biphasic insulin aspart 30; b.i.d.=twice a day; BMI=body mass index; HbA_{1c}=glycohemoglobin; q.d.=once a day. IGlarg=insulin glargine.
*Between-treatment difference not statistically significant ($P \geq 0.05$).

Costs and Perspective

The cost-effectiveness analysis was performed from a direct medical cost perspective that captured hospital costs, pharmacy costs, and patient out-of-pocket costs. Indirect costs (due to time off work and death before retirement age) were excluded. All costs are reported in 2008 Chinese Yuan (CNY). A survey of 54 physicians in nine hospitals in Beijing and Chengdu was performed to gather cost data for each of the complications simulated by the CORE Diabetes Model. Hospitals are the basic unit for healthcare provision in China. These diabetes-related complication costs have been previously described.[5] The costs were collected in 2007 and were inflated to 2008 values.[29] Costs of insulin and concomitant OADs were based on recorded usage in the OnceMix and INITIATE studies (Table 3). Insulin costs were based on the Chinese price of the FlexPen® device (Novo Nordisk, Bagsværd, Denmark) for BIAsp 30 (CNY 93.55) and the SoloSTAR® device (Sanofi-aventis, Paris, France) for IGlarg (CNY 268.00); both devices contain 300 international units. It was assumed that patients performed self-monitoring of blood glucose with a test frequency of 0.78 strips per day (CNY 2310 per year).

Discounting and Time Horizon

Discounting of future costs and clinical outcomes (in terms of life years) was performed, with a discount rate of 3% per annum applied in the base case analysis, based on WHO guidelines for cost-effectiveness analysis.[30] The computer simulations were performed over time horizons of 30 years, in order to fully capture mortality and the incidence of late-stage complications.

Health-Related Quality of Life

Quality-adjusted life years (QALYs) were calculated in the cost-effectiveness analysis. Health state utility and event disutility values were applied, and were dependent on the complication status of each simulated patient. Health state utilities and event disutilities were based on values reported in the UKPDS,[31] supplemented with data from other sources.[32-34] Disutilities for hypoglycemic events were also

Table 3. Medication usage based on the OnceMix and INITIATE studies and associated costs for China.

OnceMix	**BIAsp 30 q.d.**	**IGlarg q.d.**
End-of-study insulin usage, IU/day	25.31	22.91
Annual insulin costs, CNY	2882.42	7475.02
Sulfonylurea usage (1 mg t.i.d.), %	100	100
Metformin usage (2000 mg q.d.), %	100	100
Annual OAD costs, CNY	3489.97	3489.97
Total annual medication costs, CNY	6372.39	10,964.99
INITIATE	**BIAsp 30 b.i.d.**	**IGlarg q.d.**
End-of-study insulin usage, IU/day	78.72	51.37
Annual insulin costs, CNY	8965.02	16,760.89
Thiazolidinedione usage (15 mg q.d.), %	32	32
Metformin usage (2,000 mg q.d.), %	100	100
Annual OAD costs, CNY	1896.93	1896.93
Total annual medication costs, CNY	10,861.95	18,657.82

BIAsp 30=biphasic insulin aspart 30; b.i.d.=twice a day; CNY=Chinese Yuan; IGlarg=insulin glargine; IU=international unit; OAD=oral antidiabetic; q.d.=once a day; t.i.d.=three times a day.

applied, with a value of –0.0035 for each minor event and a value of –0.0118 for each event requiring the assistance of another person (major events); both values capture the fear associated with hypoglycemia.[35]

Sensitivity Analysis

A series of one-way sensitivity analyses were performed to assess the impact of varying key input parameters on final outcomes. In the base case, a discount rate of 3% per year was applied to future costs and life years; a sensitivity analysis assessed the impact of applying a discount rate of 6% for costs and 0% for life years, based on WHO recommendations.[30] To address uncertainty around the cost data that were collected in Chinese hospitals, two separate sensitivity analyses assessed the impact of such costs being either 20% greater than or 20% less than the base case values. Sensitivity analyses were also performed over 5-, 10-, and 20-year time horizons (vs. a 30-year time horizon used in the base case). Chinese patients with diabetes may have a high prevalence of microalbuminuria;[21] therefore, sensitivity analyses were performed where 22.8% of the simulated cohorts had microalbuminuria at baseline,[5] compared with 5.5% and 4.0% in the OnceMix and INITIATE studies. The use of Framingham Heart Study or UKPDS-derived risk equations may lead to overestimations of cardiovascular events in Asian populations.[36,37] Therefore, in a sensitivity analysis, the risk of first stroke was reduced by 50% compared with UKPDS Risk Engine-predicted events,[37] and the risks of other cardiovascular complications (including the onset of congestive heart failure or unstable angina) were reduced by 63%-64% compared with Framingham Heart Study-predicted events.[36]

Statistical Methodology

Monte Carlo simulation techniques were used to calculate cost-effectiveness outcomes. A cohort of 1000 patients was run through the

Figure 1. Scatter plot of incremental costs and effects for once-daily BIAsp 30 versus IGlarg based on the OnceMix study. BIAsp 30=biphasic insulin aspart 30; CNY=Chinese Yuan; IGlarg=insulin glargine.

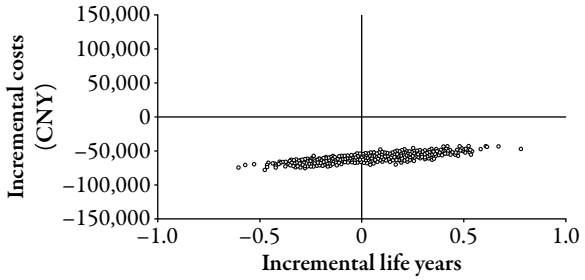
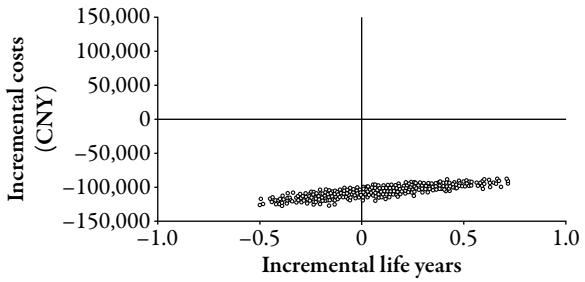


Figure 2. Scatter plot of incremental costs and effects for twice-daily BIAsp 30 versus IGlarg based on the INITIATE study. BIAsp 30=biphasic insulin aspart 30; CNY=Chinese Yuan; IGlarg=insulin glargine.



model 1000 times for each simulation, with mean values and standard deviations generated using a nonparametric bootstrapping approach.[38] One thousand mean values (each of 1000 patients) of incremental costs and incremental effectiveness, in terms of life expectancy, were plotted on cost-effectiveness planes for the base case results from the OnceMix analysis (Figure 1) and the INITIATE analysis (Figure 2). In the scatter plots, the origins represent the comparator therapy for each analysis (IGlarg based on OnceMix or INITIATE) and the dots represent the incremental costs and effects of either once-daily BIAsp 30 based on OnceMix or twice-daily BIAsp 30 based on INITIATE.

RESULTS

Once-Daily Biphasic Insulin Aspart 30 versus Insulin Glargine Based on OnceMix

Modeling indicated that once-daily BIAsp 30 would increase undiscounted life expectancy by 0.07 life years compared with IGlarg (16.64 vs. 16.57 life years; Table 4). When clinical outcomes were discounted, once-daily BIAsp 30 improved life expectancy by 0.04 years compared with IGlarg (12.37 vs. 12.33 years). The cumulative incidences of most simulated microvascular and macrovascular complications were reduced (Table 4), driven by lower HbA_{1c} levels for patients receiving once-daily BIAsp 30 compared with IGlarg.

It was also projected that treatment with once-daily BIAsp 30 would reduce direct medical costs compared with treatment with IGlarg; cost savings of CNY 59,710 per patient were calculated (CNY 229,991 vs. CNY 289,621 per patient; Table 4). The projected cost savings for BIAsp 30 were driven by lower lifetime treatment costs (CNY 111,710 vs. CNY 170,802 per patient). Diabetes-related complication costs were lower for once-daily BIAsp 30 with the exception of hypoglycemia-related costs. Lifetime management costs for patients were higher for patients receiving once-daily BIAsp 30, due to improved life expectancy compared with IGlarg.

Twice-Daily Biphasic Insulin Aspart 30 versus Insulin Glargine Based on INITIATE

Modeling indicated that twice-daily BIAsp 30 would increase undiscounted life expectancy by 0.14 life years compared with IGlarg (17.75 vs. 17.61 life years; Table 5). When clinical outcomes were discounted, twice-daily BIAsp 30 improved life expectancy by 0.08 years compared with

Table 4. Base case results for once-daily BIAsp 30 versus IGlarg based on the OnceMix study.

Summary clinical outcomes	**BIAsp 30 q.d.**	**IGlarg q.d.**
Undiscounted life expectancy, years	16.64	16.57
Discounted life expectancy, years	12.37	12.33
Quality-adjusted life expectancy, years	8.32	8.35
Cumulative incidence of complications, %	**BIAsp 30 q.d.**	**IGlarg q.d.**
Background retinopathy	21.48	21.96
Proliferative retinopathy	8.58	8.92
Macular edema	18.44	18.89
Severe vision loss	9.04	9.22
Cataract	10.41	10.46
Microalbuminuria	21.81	22.47
Gross proteinuria	6.17	6.42
End-stage renal disease	0.87	0.95
Nephropathy-related death	0.27	0.30
Foot ulcer, first	36.22	36.46
Foot ulcer, recurrence	47.46	48.18
Amputation	10.40	10.60
Neuropathy	55.69	56.35
Peripheral vascular disease	11.16	11.38
Congestive heart failure, onset	23.88	24.10
Congestive heart failure, death	12.83	12.95
Angina	13.57	13.57
Myocardial infarction, event	18.64	18.90
Myocardial infarction, death	12.71	12.97
Stroke, event	26.04	26.21
Stroke, death	13.71	13.81
Summary cost outcomes	**BIAsp 30 q.d.**	**IGlarg q.d.**
Direct medical costs, CNY	229,911	289,621
Treatment	111,710	170,802
Patient management	34,681	34,565
Cardiovascular disease	41,567	41,808
Renal disease	1418	1519
Diabetic foot and neuropathy	37,865	38,203
Eye disease	2516	2576
Hypoglycemia	153	147

BIAsp 30=biphasic insulin aspart 30; CNY=Chinese Yuan; IGlarg=insulin glargine; q.d.=once a day
Values shown are means.

Table 5. Base case results for twice-daily BIAsp 30 versus IGlarg based on the INITIATE study.

Summary clinical outcomes	**BIAsp 30 b.i.d.**	**IGlarg q.d.**
Undiscounted life expectancy, years	17.75	17.61
Discounted life expectancy, years	12.99	12.91
Quality-adjusted life expectancy, years	8.95	8.96
Cumulative incidence of complications, %	**BIAsp 30 b.i.d.**	**IGlarg q.d.**
Background retinopathy	21.14	22.73
Proliferative retinopathy	5.84	6.63
Macular edema	17.96	19.38
Severe vision loss	8.08	8.88
Cataract	10.41	10.70
Microalbuminuria	21.51	23.27
Gross proteinuria	5.78	6.65
End-stage renal disease	1.67	1.90
Nephropathy-related death	0.69	0.78
Foot ulcer, first	36.05	36.95
Foot ulcer, recurrence	48.83	49.84
Amputation	10.53	10.83
Neuropathy	55.58	57.98
Peripheral vascular disease	14.02	14.84
Congestive heart failure, onset	25.82	26.09
Congestive heart failure, death	13.44	13.47
Angina	21.94	21.92
Myocardial infarction, event	18.01	18.89
Myocardial infarction, death	13.99	14.45
Stroke, event	23.55	23.61
Stroke, death	12.39	12.29
Summary cost outcomes	**BIAsp 30 b.i.d.**	**IGlarg q.d.**
Direct medical costs, CNY	303,142	410,491
Treatment	178,320	282,623
Patient management	36,157	36,068
Cardiovascular disease	43,376	44,444
Renal disease	3838	4278
Diabetic foot and neuropathy	39,100	40,413
Eye disease	2350	2572
Hypoglycemia	0	94

BIAsp 30=biphasic insulin aspart 30; b.i.d.=twice a day; CNY=Chinese Yuan; IGlarg=insulin glargine; q.d.=once a day. Values shown are means.

IGlarg (12.99 vs. 12.91 years). The cumulative incidences of most simulated microvascular and macrovascular complications were reduced (Table 5), driven by lower HbA_{1c} levels for patients receiving twice-daily BIAsp 30 compared with IGlarg.

It was also projected that treatment with twice-daily BIAsp 30 would reduce direct medical costs compared with treatment with IGlarg; cost savings of CNY 107,349 per patient were calculated (CNY 303,142 vs. CNY 410,491 per patient; Table 5). The projected cost savings for BIAsp 30 were driven by lower lifetime treatment costs (CNY 178,320 vs. CNY 282,623 per patient). Diabetes-related complication costs were lower for twice-daily BIAsp 30 but lifetime management costs for patients were higher.

Evaluation of Cost-Effectiveness

Once-daily BIAsp 30 and twice-daily BIAsp 30 were both projected to be more effective (in terms of life expectancy) and less costly than IGlarg, based on the respective OnceMix and INITIATE modeling analyses. Plotting incremental costs versus incremental effectiveness (in terms of life expectancy) for once-daily BIAsp 30 versus IGlarg based on OnceMix and twice-daily BIAsp 30 versus IGlarg based on INITIATE indicated that, in both comparisons, all 1000 points, each representing mean values from a cohort of 1000 simulated patients, were located on the bottom halves of the cost-effectiveness planes (Figures 1 and 2).

Quality-Adjusted Life Expectancy

When health state utilities and event disutilities were applied in the simulations, BIAsp 30 was less effective than IGlarg in the modeling analyses. Quality-adjusted life expectancy for once-daily BIAsp 30 was projected to be 8.32 QALYs compared with 8.35 QALYs for IGlarg (based on OnceMix). Quality-adjusted life expectancy for twice-daily BIAsp 30 was 8.95 QALYs compared with 8.96 QALYs for IGlarg (based on INITIATE). In both cases lower-quality-adjusted life expectancy for BIAsp 30 was due to increased lifetime hypoglycemia and its associated disutility (Tables 4 and 5).

Sensitivity Analysis

Results of a series of one-way sensitivity analyses revealed that cost savings for BIAsp 30 were sensitive to the time horizons and discount rates applied in the simulations. When the discount rate for costs was set to 6% per annum (vs. 3% in the base case), cost savings were reduced to CNY 46,227 per patient for once-daily BIAsp 30 (vs. CNY 59,710 in the base case) and to CNY 82,190 per patient for twice-daily BIAsp 30 (vs. CNY 107,350 in the base case). Simulations performed over shorter time horizons also reduced the cost savings for once-daily and twice-daily BIAsp 30; a 5-year time horizon led to cost savings of CNY 20,779 per patient for once-daily BIAsp 30 (based on OnceMix) and CNY 35,469 per patient for twice-daily BIAsp 30 (based on INITIATE). When the complication costs were either increased by 20% or decreased by 20%, overall cost savings for BIAsp 30 changed by less than 1% compared with the base case, suggesting that the projected savings were largely attributable to the lower price of BIAsp 30 compared with IGlarg in China.

In all sensitivity analyses, BIAsp 30 was more effective in terms of life expectancy compared with IGlarg. When the baseline prevalence of microalbuminuria was set to 22.8% (vs. 5.5% and 4.0% for the once-daily BIAsp 30 and twice-daily BIAsp 30 base case analyses, respectively), improvements in life expectancy

were 0.06 years for once-daily BIAsp 30 (vs. an improvement of 0.07 years in the OnceMix base case) and 0.18 years for twice-daily BIAsp 30 (vs. an improvement of 0.14 years in the INITIATE base case). When Asian population-specific cardiovascular event risks were applied in the simulations, large increases in life expectancy for both BIAsp 30 and IGlarg were projected compared with the base case, but improvements in life expectancy for BIAsp 30 versus IGlarg were reduced. In this modeled scenario, life expectancy was 18.50 years for once-daily BIAsp 30 and 18.48 years for IGlarg (vs. 16.64 and 16.57 years in the base case), and for twice-daily BIAsp 30 life expectancy was 19.59 years compared with 19.47 years for IGlarg (vs. 17.75 and 17.61 years in the base case). Cost savings for BIAsp 30 were increased in each scenario to CNY 65,203 and CNY 115,319 per patient, respectively, compared with cost savings of CNY 59,710 and CNY 107,349 in the corresponding base case analyses.

DISCUSSION

The present modeling analysis conducted in the Chinese setting, based on data from the OnceMix and INITIATE studies, indicated that initiating insulin therapy with BIAsp 30, either once or twice daily, was projected to delay the onset of complications and increase life expectancy when compared with IGlarg in patients with type 2 diabetes. Cost savings were also projected due to the substantially lower price of BIAsp 30 in China; sensitivity analysis revealed that this factor was the main driver of cost savings. In health economic terms, BIAsp 30 is the dominant therapy for patients with type 2 diabetes initiating insulin in China as BIAsp 30 was projected to be both life extending and cost saving compared with IGlarg.

The cost-effectiveness analysis based on the INITIATE study, where BIAsp 30 was used twice daily, indicated greater projected cost savings compared with the cost-effectiveness analysis based on the OnceMix study, where BIAsp 30 was used once daily. This was due to higher projected life expectancy in the INITIATE-based analysis due to younger patient age at baseline (mean of 52 years vs. 56 years in OnceMix), resulting in the capture of cost savings over a longer duration. As patients with type 2 diabetes in China develop the disease at younger ages than their Western counterparts,[39] and may also have lower body mass and earlier insulin secretory deficits,[40,41] the projected lifetime cost savings for BIAsp 30 may have been underestimated in this analysis.

A cost-effectiveness comparison of twice-daily BIAsp 30 with once-daily BIAsp 30 has not been performed. Patients initiating insulin therapy with once-daily BIAsp 30 may inevitably be moved to a twice-daily regimen to meet exogenous insulin requirements. The 1-2-3 study assessed the efficacy of once-daily BIAsp 30, followed by twice-daily BIAsp 30 after 16 weeks if HbA_{1c} targets were not met, and then thrice-daily BIAsp 30 after an additional 16 weeks for patients that did not reach target on a twice-daily regimen.[42] After 16 weeks, 41% of patients receiving once-daily BIAsp 30 reached the American Diabetes Association HbA_{1c} target (<7.0%), with the remaining patients subsequently moved to twice-daily BIAsp 30, where 70% of such patients reached the target. Based on the 1-2-3 study, twice-daily BIAsp 30 may be the appropriate regimen for insulin initiation. Future modeling analyses could assess the potential cost and clinical implications of initiating insulin with a once-daily regimen and only moving to twice-daily therapy when required. Observational data reflecting routine clinical practice may enable relevant cost-effectiveness analyses to be performed.

This was the second application of the CORE Diabetes Model to the Chinese setting. Much of the clinical data in the model, in the form of multivariate regression formulae that predict event risk, equations that describe the progression in physiological parameters over time, and risk multipliers that link complication submodels and capture data regarding multifactorial interventions (eg, the impact of statins, aspirin, and ACEI), are derived from interventional and observational studies performed in predominantly Western populations. This was a limitation of the modeling analysis. Additionally, the modeling of increased cardiovascular risk for patients with microalbuminuria and gross proteinuria may have resulted in overestimations of these cardiovascular complications; renal status was not a parameter in the cardiovascular risk models utilized.[15] In the absence of long-term studies in China on the scale of the Framingham Heart Study and the UKPDS, this modeling analysis provided relevant estimates of long-term clinical and cost outcomes for BIAsp 30 and IGlarg. The CORE Diabetes Model has been validated against a range of external data sets, including Asian-based cohorts.[16]

The impact of adjusting Framingham Heart Study and UKPDS-derived risk equations for Asian populations was assessed. When the base case risks of cardiovascular events were lowered, projected life expectancy increased for all simulated patients, and the projected lifetime cost savings for once-daily and twice-daily BIAsp 30 increased compared with the base case, despite reduced improvements in life expectancy for BIAsp 30 versus IGlarg. The implementation of multivariate regression formulae from the Hong Kong Diabetes Registry[37,43] and other sources[44,45] may better capture China-specific cardiovascular event risk in future analyses.

CONCLUSION

This modeling analysis has indicated that for patients with type 2 diabetes in China who commenced insulin therapy with BIAsp 30, either once or twice daily, improvements in life expectancy were projected compared with patients who commenced insulin therapy with IGlarg. Owing to the lower price of BIAsp 30 in China, substantial lifetime cost savings were also projected.

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