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ORIGINAL RESEARCH

Cost-Effectiveness of Switching to Biphasic Insulin Aspart in Poorly-Controlled Type 2 Diabetes Patients in China

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ABSTRACT

Introduction: Type 2 diabetes is an increasing problem in China, yet there is a paucity of data regarding the cost-effectiveness of pharmacological interventions in the Chinese setting.
Methods: Previous data were obtained from PRESENT (Physicians' Rou-

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tine Evaluation of Safety and Efficacy of NovoMix 30 Therapy), a multicountry, single-arm, observational study where type 2 diabetes patients poorly controlled with biphasic human insulin (BHI) were converted to biphasic insulin aspart 30 (BIAsp30); the Chinese subgroup experienced an improvement in HbA_{1c} and a reduction in hypoglycaemic events. A published and validated computer simulation model of diabetes (the CORE Diabetes Model) was used to estimate the long-term clinical and cost consequences of switching to BIAsp30 from BHI in the Chinese setting. Treatment effects and patient characteristics were derived from PRESENT and country-specific published sources. Primary research was performed to ascertain patient management practices and diabetes-related complication costs. Risks of modelled complications were derived from landmark clinical trials and epidemiological studies. Costs and clinical projections were made over patient lifetimes from a third-party payer perspective and discounted at 3% annually. Extensive sensitivity analyses were performed.

Results: Conversion to BIAsp30 from BHI was projected to improve discounted life expectancy by 0.38 years per patient (9.91 vs 9.53 years) and quality-adjusted life expectancy by 0.91 quality-adjusted life years (QALYs) per patient (6.32 vs 5.41 QALYs). Conversion to BIAsp30 was associated with increased direct medical costs of Chinese Yuan (CNY) 1751 per patient, due to higher pharmacy and management costs (CNY +19,007), offset by reduced diabetes-related complication costs (CNY –17,254) over patient lifetimes. BIAsp30 was associated with an incremental cost-effectiveness ratio of CNY 1926 per QALY gained.

Conclusion: BIAsp30 was projected to substantially improve clinical outcomes but was associated with increased lifetime medical costs. BIAsp30 would be considered cost-effective in China given a willingness-to-pay threshold of CNY 100,000 per QALY gained in type 2 diabetes patients poorly controlled on BHI.

Keywords: aspart; biphasic; China; cost-effectiveness; insulin; modelling; type 2 diabetes

INTRODUCTION

Diabetes mellitus is a serious challenge to healthcare systems and is the fifth leading cause of death worldwide.[1] The high prevalence of the disease provides an indication of the challenge presented by diabetes, with Wild et al. estimating the global prevalence at 171 million patients in 2000 and forecasting a prevalence in developing countries of 298 million cases by 2030.[2] The developing world will shoulder a

growing share of the diabetes burden, with 75% of people with diabetes predicted to reside in developing countries by 2025, compared with only 62% in 1995.[3] It is estimated that healthcare systems in India and China will be challenged by an additional 48.5 million cases of diabetes between 2007 and 2025.[4]

In China, the increasing prevalence of diabetes is occurring as part of a shift in disease patterns from communicable diseases to lifestyle-related illnesses, which has accompanied rapid economic development.[5] For example, mortality rates for acute infectious diseases decreased in China from 34.32 deaths per 100,000 person years in 1975 to 1.15 deaths in 1990.[6] Currently, around 80% of deaths in China are attributable to chronic illnesses such as diabetes and cardiovascular disease.[7]

The prevalence rate of diabetes in Shanghai (both diagnosed and undiagnosed) has been estimated by Jia and colleagues at 6.87%, with 40% of cases undiagnosed.[8] The prevalence rate in the population over 50 years of age in Qingdao, Shandong Province, was estimated as 10% in a study by Dong and colleagues.[9] While these two studies were based on data from relatively affluent coastal regions, the rapid urbanisation that is accompanying China's economic development makes these observations all the more pertinent. Diabetes in China will have a substantial impact on productivity. The World Health Organization (WHO) has noted that most people with diabetes in developing countries are middle-aged, whereas in developed nations diabetes predominantly affects patients who have either left the workforce or are close to retirement.[10] Chan et al. suggest that the main increase in diabetes prevalence in China will occur in the 45–54 year old group, during the most productive working years.[11]

The impact of diabetes on healthcare costs in developed countries is well known. In the United States, healthcare costs for individuals with diabetes were as much as five times greater than those without diabetes in 1997.[12] In Europe, the CODE-2 study revealed that hospitalisation costs contributed 55% of all direct medical costs attributable to patients with type 2 diabetes, with insulin and other antidiabetic pharmacy costs amounting to 7%.[13] Thus, complication costs account for the largest share of the total medical cost burden attributable to patients with type 2 diabetes.

Estimation of the financial impact of diabetes in China is hindered by a paucity of available studies on diabetes complication costs. One study conducted in eleven large cities in China estimated costs for 2002,[14] and a recent health economic analysis has published diabetes cost data for Beijing,[15] but a broader cross-country cost profile for China is not available. Despite the scarcity of information on diabetes-related costs in China, it is likely that a greater proportion of available resources are directed at treating costly complications after they have developed. This is similar to the pattern experienced by healthcare providers in Western countries, where the high medical costs of diabetes are largely attributable to its complications.[16] For example, in Europe it is known that type 2 diabetes is the leading cause of end-stage renal disease (ESRD),[17] which is associated with substantial medical costs.[18]

International clinical guidelines state that the primary goal in the treatment of diabetes is effective glycaemic control.[19] Landmark epidemiological studies and clinical trials have shown that maintaining good glycaemic control is associated with reduced incidence of diabetes-related complications in type 2 diabetes.[20,21] The UK Prospective Diabetes Study (UKPDS) demonstrated that intensive treatment with sulphonylureas or insulin, aimed at lowering fasting plasma glucose to below 6 mmol/l, resulted in a 12% reduction in the risk of diabetes-related complications, and a 10% risk reduction for diabetes-related death compared with conventional treatment in predominantly white patients with type 2 diabetes, independent of the type of agent used.[21]

In type 2 diabetes patients, insulin is used when oral antidiabetic drugs (OADs) are no longer sufficient to achieve glycaemic control.[22] Biphasic insulin aspart 30 (BIAsp30; NovoMix®, Novo Nordisk A/S, Bagsværd, Denmark) is a modern analogue insulin mix of 30% rapid-acting soluble insulin aspart and 70% intermediate-acting insulin aspart crystallised with protamine. In clinical trial settings, analogue insulins have not demonstrated significant improvements in glycaemic control for type 2 diabetes.[23] However, intrapatient blood glucose variability is lower in modern insulins compared with older human insulins.[24,25] Furthermore, a recent Cochrane review of short-acting insulin analogues revealed a trend towards significant reductions in hypoglycaemic events (on average −0.2 episodes per patient per month [95% CI: −0.5, 0.1]) versus human insulins in type 2 diabetes.[26]

The Physicians' Routine Evaluation of Safety and Efficacy of NovoMix 30 Therapy (PRESENT) study was an open-label, multicountry, single-arm, observational study that enrolled over 20,000 patients with type 2 diabetes, both insulin-naïve and insulin-treated, with and without concurrent OAD usage, and has been reported extensively elsewhere.[27–30] Patients in PRESENT were treated with BIAsp30 twice-daily at dosages that varied according to the discretion of their physician and were not treated to any specific glycaemic control targets. Data from the subset of patients transferred to BIAsp30 from biphasic human insulin (BHI) in China are analysed here (n=2289), where significant improvements in glycosylated haemoglobin (HbA_{1c}) levels (−1.82%; P<0.001) and substantial reductions in hypoglycaemic events (−1100 events [major and minor] per 100 patient years; P<0.001) were observed in poorly controlled patients (baseline HbA_{1c} = 8.81%) over 3 months. The aim of this analysis was to evaluate the long-term cost and clinical outcomes associated with switching this poorly controlled type 2 diabetes patient group in China to BIAsp30 from BHI, based on the results from PRESENT.

MATERIALS AND METHODS

A published and validated computer simulation model of diabetes was used to assess the cost-effectiveness of BIAsp30 in Chinese type 2 diabetes patients. Treatment effects for BIAsp30 were derived from PRESENT, with diabetes-related complication costs and patient management practices obtained from primary research in China.

Model

A brief overview of the CORE Diabetes Model is provided here, but the interested reader is referred to a previously published article by Palmer et al.[31] The model is a diabetes policy analysis tool for both type 1 and type 2 diabetes. It takes into account pharmacy, management and complication costs, screening and treatment strategies for micro- and macrovascular complications, and treatment practices for end-stage complications. Disease progression is based on a series of inter-dependent Markov submodels that simulate the progression of diabetes-related complications, including angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula oedema, cataract, hypoglycaemia, ketoacidosis, lactic acidosis, nephropathy and ESRD, neuropathy, foot ulcer and amputation, and mortality from other causes.[31] Each submodel uses time, health state, time in health state, and diabetes type-dependent probabilities derived from published sources. The reliability of simulated outcomes has been tested, with results validated against those reported by clinical trials and epidemiological studies.[32]

While the data used in the CORE Diabetes Model is derived primarily from landmark studies such as the UKPDS[21,33–38] and Framingham Heart Study,[39] conducted in largely white populations, China-specific risks of modelled events were incorporated in this analysis where data were available. Age- and sex-stratified mortality from non-diabetes-related causes (i.e. mortality attributable to causes not covered within the individual submodels of the CORE Diabetes Model) was calculated annually based on WHO life tables for China in 2005,[40] adjusted for causes of death explicitly modelled. The adjustments were based on data from the WHO Global Burden of Disease Estimates report for 2002,[41] which reports age-standardised causes of death for member countries. China-specific ESRD treatment modalities (haemodialysis, peritoneal dialysis, or renal transplant) and survival were also incorporated.[42,43] Mortality associated with hypoglycaemia was not captured in the analyses.

Treatment Effects

Treatment effects were taken from the Chinese subgroup of type 2 diabetes patients switched to BIAsp30 from BHI at their physicians' discretion in PRESENT (n=2289). Both patients who received insulin therapy exclusively and patients prescribed OADs concomitantly were included. BIAsp30 was associated with an improvement in HbA_{1c} of 1.82%-points over 3 months, which was modelled as an initial decrease from baseline levels followed by a natural progression in line with that observed in the UKPDS.[21] Body mass index (BMI) reductions and hypoglycaemic event rates (in terms of events per 100 patient years) observed in PRESENT were also applied in the simulations (Table 1).

Simulated Cohort

The baseline characteristics and risk factors of the simulated cohort were based on those of the Chinese subgroup of

Table 1. Change in HbA_{1c}, BMI and hypoglycaemic events as observed in the China subgroup of PRESENT (n=2289).

	BIAsp30
Mean change from baseline in HbA_{1c}, %-points	–1.82
Mean change from baseline in BMI, kg/m^2	–0.22
Baseline minor hypoglycaemic event rate (events per 100 patient years)	1337
End of study minor hypoglycaemic event rate (events per 100 patient years)	446
Baseline major hypoglycaemic event rate* (events per 100 patient years)	239
End of study major hypoglycaemic event rate* (events per 100 patient years)	30

Source: Novo Nordisk A/S.
*Hypoglycaemic event requiring third-party assistance.
BIAsp30=biphasic insulin aspart 30; HbA_{1c}=glycosylated haemoglobin; BMI=body mass index.

PRESENT. A virtual cohort of 1000 patients for simulation was defined (Table 2), with 57.6% being male, mean baseline age of 56.7 years, mean duration of diabetes of 6.6 years and mean HbA_{1c} level of 8.8%. Additional baseline risk factors (systolic blood pressure, serum lipids, etc) and frequency of existing complications were supplemented with data from the Shanghai Diabetes Studies[8] and other published sources.[44–46]

Costs and Perspective

The analysis was undertaken from the perspective of a third-party payer (e.g. managed care organisations, insurance companies, etc) incorporating future treatment costs, patient management costs and medical complication costs. Performing cost-effectiveness analyses from this perspective yields constructive information that can often be used to assist decision-making bodies and healthcare payers in outlining policies with regards to the use of new pharmacological interventions. The costs of lost working time due to illness and death prior to the retirement age were excluded. All costs were presented in and calculated in 2007 Chinese Yuan (CNY).

Primary research was performed by the authors to obtain data for diabetes-related complication and management costs and practices in China. A survey of physicians (n=54) was performed in two cities, Beijing and Chengdu, with four hospitals consulted in Beijing and five in Chengdu. Hospitals are the basic unit for healthcare provision in China. Hospitals were selected according to tier classification as designated by the Ministry of Health,[47] with six Tier 3 (containing the largest hospitals with specialist units) and three Tier 2 (community-based) hospitals included. Physicians were asked specific questions regarding resource use and management practices, and were required to hold the position of a deputy director or higher. Complication and management cost data were weighted by outpatient visits to provide an average value for each cost input (Table 3).

Table 2. Characteristics and complications of simulated cohort (n=1000).[8,44–46]

	Mean	SD
Patient demographics		
Baseline age, years*	56.7	11.2
Duration of diabetes, years*	6.6	4.9
Percentage male*	57.6	
Baseline risk factors		
Hba_{1c}, %*	8.8	1.6
Systolic blood pressure, mmHg	137.7	22.6
Total cholesterol, mg/dl	207.3	49.1
HDL, mg/dl	50.3	14.7
LDL, mg/dl	143.8	39.2
Triglycerides, mg/dl	219.5	202.3
Body mass index, kg/m^{2}*	24.3	2.6
	Percentage	
Racial characteristics		
Asian/Pacific Islander	100.0	
Baseline cardiovascular complications		
Myocardial infarction	2.3	
Angina	0.0	
Peripheral vascular disease	6.5	
Stroke*	5.9	
Congestive heart failure*	0.0	
Atrial fibrillation	3.0	
Left ventricular hypertrophy	3.0	
Baseline renal complications		
Microalbuminuria	22.8	
Gross proteinuria*	0.0	
End-stage renal disease	0.0	
Baseline eye complications		
Background diabetic retinopathy*	16.0	
Proliferative diabetic retinopathy*	0.0	
Severe vision loss	7.0	
Baseline macular oedema		
Macular oedema	10.5	

Table 2. Characteristics and complications of simulated cohort (n=1000)[8,44–46] ***(Continued).***

	Percentage
Baseline cataract	
Cataract	0.0
Baseline foot ulcer complications	
Uninfected ulcer*	0.0
Infected ulcer	0.0
Healed ulcer	0.0
History of amputation	1.0
Baseline neuropathy	
Neuropathy*	23.2

*Data derived from Chinese subgroup of PRESENT at baseline (Novo Nordisk A/S).
SD=standard deviation; HbA_{1c}=glycosylated haemoglobin; HDL=high-density lipoprotein; LDL=low-density lipoprotein.

Pharmacy costs were accounted for both BIAsp30 and BHI and were obtained from Novo Nordisk A/S (Table 4). The cost of OAD usage was applied equally to both treatment arms based on recorded usage in PRESENT. Blood glucose monitoring costs were derived from wholesale device costs (strips and meters) weighted by average strip use per patient derived from a separate survey performed in 150 type 2 diabetes patients in Beijing, Shanghai and Guangzhou, and were applied equally to each treatment arm.

Quality-of-Life Utilities

Quality-adjusted life expectancy was incorporated into the analysis using diabetes-related health state utility and event disutility values published by Palmer et al.[31] A disutility of –0.0035 was applied for each minor hypoglycaemic event (an event not requiring hospitalisation) recorded in the simulation. To capture reduced utility associated with major hypoglycaemic events (those requiring third-party assistance), a disutility value of –0.0118 was applied. Hypoglycaemia disutility values were derived from a published source.[48]

Discounting and Time Horizon

Discounting of future costs and clinical benefits, in terms of quality-adjusted life years (QALYs), was performed to account for both the time value of money and time preference for future health effects. While Chinese pharmacoeconomic guidelines stipulate that discounting of future costs and clinical outcomes be performed in cost-effectiveness analyses, the specific discount rates to use have not been made explicit.[49] Thus, in the base case analysis, both costs and clinical outcomes were discounted at a rate of 3% per annum, according to WHO guidelines for discounting in cost-effectiveness analysis.[50] The time horizon was set to 30 years in the base case analysis, to capture both mortality and the incidence of diabetes-related complications that may occur over patient lifetimes.

Table 3. Management and diabetes-related complication costs, calculated using physician surveys (n=54) for the year 2007 only.

	CNY
Management costs	
Annual cost of statins	2207.00
Annual cost of aspirin	227.00
Annual cost of ACE inhibitors	1681.00
Annual cost of microalbuminuria screening	381.00
Annual cost of macroalbuminuria screening	39.00
Annual cost of eye screening	59.00
Monthly cost of foot screening	186.00
Direct costs: CVD complications	
Cost of myocardial infarction, year of event	40,050.00
Cost of myocardial infarction, subsequent years	9200.00
Cost of angina, year of onset	33,592.00
Cost of angina, subsequent years	5997.00
Cost of coronary heart failure, year of onset	13,319.00
Cost of coronary heart failure, subsequent years	8096.00
Cost of stroke, year of event	15,609.00
Cost of stroke, subsequent years	7029.00
Cost of stroke, death within 30 days of event	12,097.00
Cost of peripheral vascular disease, year of onset	34,557.00
Cost of peripheral vascular disease, subsequent years	12,759.00
Direct costs: renal complications	
Cost of haemodialysis, first year	98,363.00
Cost of haemodialysis, subsequent years	79,143.00
Cost of peritoneal dialysis, first year	72,792.00
Cost of peritoneal dialysis, subsequent years	71,882.00
Cost of renal transplant, year of procedure	145,009.00
Cost of renal transplant, subsequent years	43,766.00
Direct costs: acute events	
Cost of major hypoglycaemic event	144.00
Cost of ketoacidosis event	790.00
Cost of lactic acidosis event	1893.00

Table 3. Management and diabetes-related complication costs, calculated using physician surveys (n=54) for the year 2007 only ***(Continued).***

	CNY
Direct costs: eye disease	
Cost of laser treatment procedure	2633.00
Cost of cataract operation, year of procedure	5407.00
Cost of cataract operation, subsequent years	156.00
Cost of blindness, year of onset	4225.00
Cost of blindness, subsequent years	1145.00
Direct costs: other complications	
Cost of neuropathy, year of onset	8878.00
Cost of neuropathy, subsequent years	5144.00
Cost of amputation event	5643.00
Cost of prosthesis following amputation event	16,989.00
Monthly cost of treating uninfected ulcer	2445.00
Monthly cost of treating infected ulcer	4132.00
Annual cost of gangrene management	45,156.00
Annual cost after ulcer healed	4200.00

Source: primary research. Values shown are means.
CNY=Chinese Yuan; ACE=angiotensin-converting enzyme; CVD=cardiovascular disease.

Table 4. Medication usage in the Chinese PRESENT subgroup and annual treatment costs.

	BIAsp30	BHI
Insulin dosage, IU/day	33.59	32.83
OAD usage, % patients		
Alpha-glucosidase inhibitors	5.7	5.7
Thiazolidinediones	3.8	3.8
Biguanides	9.3	9.3
Meglitinides	1.2	1.2
No OAD usage	80.0	80.0
Total insulin costs, CNY	3825.80	2300.70
Total OAD costs, CNY	502.10	502.10
Total SMBG costs, CNY	2291.69	2291.69
Total annual costs, CNY	6619.60	5094.49

Source: primary research and Novo Nordisk A/S.
BIAsp30=biphasic insulin aspart 30; BHI=biphasic human insulin; IU=international units; OAD=oral antidiabetic drug; CNY=Chinese Yuan; SMBG=self-management of blood glucose.

Sensitivity Analyses

Several one-way sensitivity analyses were performed to assess the effect of varying key model parameters on final outcomes. To explore uncertainty around the cost data collected by primary research, two analyses were performed where the complication and management costs were increased and decreased by 20%, respectively. The impact of discounting on final outcomes was also assessed in a separate sensitivity analysis by discounting costs at 6% per annum and not discounting QALYs. The time horizons were also varied to assess the projected outcomes over periods shorter than patient lifetimes, with results at 10 and 20 years reported. To assess the impact of reduced hypoglycaemic events for BIAsp30 compared with BHI (captured in the base case), a sensitivity analysis was performed where the hypoglycaemic event rates (both major and minor) for BIAsp30 were set equal to that of BHI. Additionally, an exploratory sensitivity analysis was performed using risks of cardiovascular events specifically adapted for Asian populations, using published data from Barzi et al.[51]

A series of analyses were performed to assess the sensitivity of BIAsp30-associated HbA_{1c} reductions on final outcomes. Five one-way sensitivity analyses were performed where the HbA_{1c} reduction was divided into five intervals, from 1.82% (as used in the base case and observed in PRESENT) to 0.00%. The lowest value used in this sensitivity analysis was equal to the weighted mean difference in HbA_{1c} reduction (0.0% [95% CI: −0.1, 0.0]) reported in a recent Cochrane review of analogue versus human insulins.[26]

Statistical Methodology

A simulated cohort of 1000 patients were run through the model 1000 times for each simulation and mean values and standard deviations were generated using a non-parametric bootstrapping approach.[52] One thousand mean values (each of 1000 patients) of incremental costs and incremental effectiveness in terms of quality-adjusted life expectancy were plotted on a cost-effectiveness plane (Figure 1).

Willingness-to-Pay

The WHO recommends that the maximum value placed on a year of perfect health in a developing country should be no greater than three times the annual income per capita.[53] With gross domestic production per capita for China in 2007 at CNY 40,333,[54] we used a willingness-to-pay (WTP) threshold in this analysis of CNY 100,000 per QALY gained to determine the likelihood of BIAsp30 being considered cost-effective in China. Our WTP threshold lies between the values applied in two recent cost-utility analyses performed in the Chinese setting.[15,55] A cost-effectiveness acceptability curve was generated to assess the likelihood of BIAsp30 being considered value for money over a range of WTP thresholds based on quality-adjusted life expectancy (Figure 2).

Figure 1. Scatter plot of change in costs versus change in quality-adjusted life expectancy for BIAsp30 versus BHI. BHI=biphasic human insulin; BIAsp30=biphasic insulin aspart 30; CNY=Chinese Yuan; QALY=quality-adjusted life year.

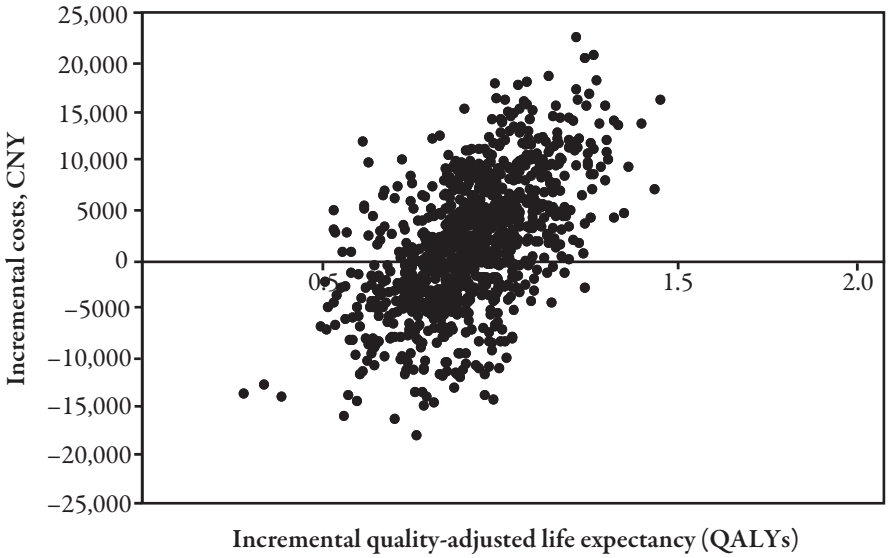
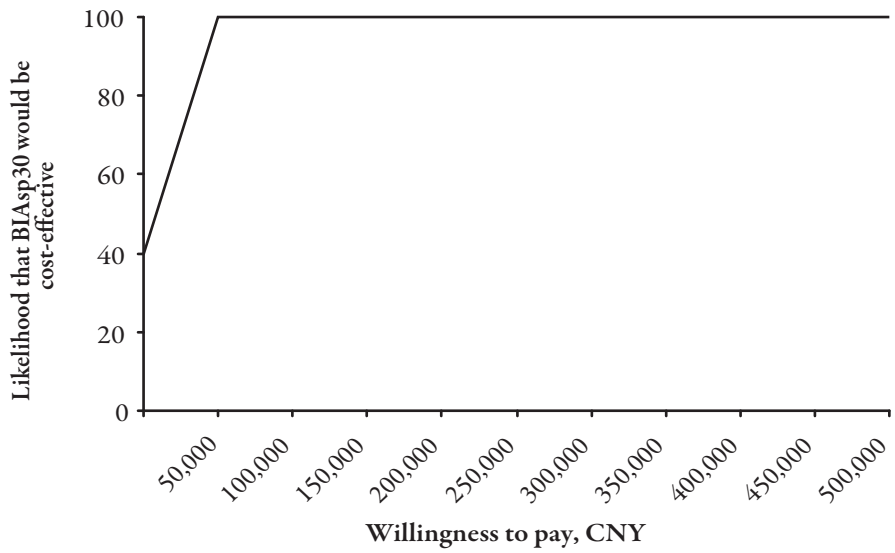


Figure 2. Cost-effectiveness acceptability curve based on quality-adjusted life expectancy. BIAsp30=biphasic insulin aspart 30; CNY=Chinese Yuan.



RESULTS

Clinical Outcomes

BIAsp30 was associated with improvements in discounted life expectancy of 0.38 years per patient compared with BHI (9.91±0.18 vs 9.53±0.18 years) over patient lifetimes (Table 5). When health-related quality of life was captured in the analysis, BIAsp30 was associated with a substantial increase in quality-adjusted life expectancy of 0.91 QALYs per patient compared with BHI (6.32±0.12 vs 5.41±0.11 QALYs).

Patients treated with BIAsp30 had a reduced cumulative incidence of most diabetes-related complications compared with patients treated with BHI (Table 6). Notable reductions were projected for all eye complications, with a 36% risk reduction in the incidence of proliferative retinopathy. There were substantial reductions in the incidence of renal complications, with a 35% risk reduction in the incidence of ESRD, a complication associated with substantial patient morbidity and high medical costs.[56]

The incidence of most cardiovascular complications was reduced for patients

Table 5. Summary of costs and clinical outcomes between two diabetes treatments, BIAsp30 and BHI, over patient lifetimes.

Cost outcomes	**BIAsp30**	**BHI**
Total costs, CNY	203,126 (4644)	201,376 (5252)
Treatment and management costs, CNY	99,402	80,395
Complication costs, CNY	103,726	120,980
Cardiovascular	62,815	66,821
Nephropathy and ESRD	11,419	17,970
Ulcer, amputation and neuropathy	26,183	29,099
Retinopathy	1898	2577
Hypoglycaemia	1331	4513
Clinical outcomes		
Life expectancy, years	9.91 (0.18)	9.53 (0.18)
Quality-adjusted life expectancy, QALYs	6.32 (0.12)	5.41 (0.11)
Cost-effectiveness outcomes		
Difference in costs between BIAsp30 and BHI	CNY 1751	
Difference in life years between BIAsp30 and BHI	0.38 life years	
Difference in QALYs between BIAsp30 and BHI	0.91 QALYs	
ICER for BIAsp30 based on life expectancy	**CNY 4654 per life year gained**	
ICER for BIAsp30 based on quality-adjusted life expectancy	**CNY 1926 per QALY gained**	

Values shown are means with standard deviations in parentheses; numerical discrepancies are due to rounding.
BIAsp30=biphasic insulin aspart 30;BHI=biphasic human insulin; CNY=Chinese Yuan; ESRD=end-stage renal disease; QALY=quality-adjusted life year; ICER=incremental cost-effectiveness ratio.

Table 6. Cumulative incidence of diabetes-related complications over patient lifetimes.

	BIAsp30	BHI	Relative difference, %
Eye complications			
Background retinopathy, %	13.09 (1.23)	18.27 (1.43)	–28.35
Proliferative retinopathy, %	0.81 (0.28)	1.27 (0.38)	–36.22
Severe vision loss, %	6.03 (0.75)	8.41 (0.86)	–28.30
Macular oedema, %	12.67 (1.03)	17.72 (1.22)	–28.50
Cataract, %	7.66 (0.91)	8.73 (0.89)	–12.26
Renal complications			
Microalbuminuria, %	14.39 (1.91)	20.27 (2.08)	–29.01
Gross proteinuria, %	12.60 (1.14)	17.68 (1.42)	–28.73
End-stage renal disease, %	4.92 (0.71)	7.61 (0.84)	–35.35
Nephropathy-related death, %	2.35 (0.47)	3.86 (0.63)	–39.12
Foot complications			
Foot ulcer (first), %	26.56 (1.42)	29.13 (1.40)	–8.82
Foot ulcer (recurrence), %	44.22 (3.35)	46.19 (3.51)	–4.26
First amputation, %	9.70 (1.05)	10.10 (1.07)	–3.96
Recurrent amputation, %	3.58 (0.77)	3.58 (0.76)	0.00
Neuropathic complications			
Neuropathy (onset), %	41.28 (1.82)	50.14 (1.92)	–17.67
Cardiovascular complications			
Peripheral vascular disease (onset), %	9.53 (0.95)	12.65 (1.06)	–24.66
Congestive heart failure (first event), %	26.58 (1.69)	28.94 (1.78)	–8.15
Congestive heart failure (death), %	27.78 (1.41)	28.86 (1.40)	–3.74
Angina, %	12.29 (1.04)	12.79 (1.06)	–3.91
Myocardial infarction (event), %	19.50 (1.23)	23.22 (1.36)	–16.02
Myocardial infarction (death), %	10.97 (0.94)	12.73 (1.05)	–13.83
Stroke (event), %	10.11 (0.93)	9.53 (0.92)	+6.09
Stroke (death), %	5.31 (0.72)	5.01 (0.68)	+5.99

Relative differences are expressed as a percentage and calculated as the difference between BIAsp30 and BHI relative to total BHI incidence. Values shown are means with standard deviations in parentheses. BHI=biphasic human insulin; BIAsp30=biphasic insulin aspart 30.

on BIAsp30. The incidences of congestive heart failure and myocardial infarction were reduced by 8% and 16%, respectively. However, more stroke events were projected for patients treated with BIAsp30, with a 6% increase in the cumulative incidence of stroke events. The increased lifetime risk of stroke for patients switched to BIAsp30 can be explained by the incorporation of data from UKPDS 60[37] for the calculation of first stroke, where HbA_{1c} was found not to be an independent risk factor for stroke, with the main drivers of stroke risk being patient age and the duration of diabetes.

Cost Outcomes

Treatment with BIAsp30 was associated with increased lifetime direct medical costs compared with BHI due to higher pharmacy and management costs, which were largely offset by lower diabetes-related complication costs. Direct medical costs over patient lifetimes were CNY 1751 higher per patient for BIAsp30 versus BHI (CNY 203,126±4644 vs CNY 201,376±5252; Table 5). Further analysis of cost outcomes revealed that, compared with continuing on BHI, treatment with BIAsp30 was associated with a 14% reduction in all diabetes-related complication costs, including a 6% reduction in cardiovascular costs, a 36% reduction in renal-related costs and a 71% reduction in costs associated with hypoglycaemic events. Lifetime treatment and management costs (insulin, concomitant medications, screening programmes, etc) were 24% higher than BHI, due to both increased life expectancy for patients on BIAsp30, resulting in a longer duration of treatment, and the higher pharmacy cost of BIAsp30.

Evaluation of Cost-Effectiveness

Treatment with BIAsp30 was associated with an incremental cost-effectiveness ratio (ICER) based on life expectancy of CNY 4654 per life year gained from a third-party payer perspective. When quality-of-life utilities were incorporated in the analysis to capture patient morbidity, BIAsp30 was associated with an ICER based on quality-adjusted life expectancy of CNY 1926 per QALY gained. Plotting incremental costs versus incremental effectiveness (in terms of quality-adjusted life expectancy) for BIAsp30 versus BHI for each of the outcomes from the 1000 patients simulated 1000 times each in the model showed that the points were distributed between the upper and lower right quadrants of the cost-effectiveness plane (Figure 1).

A cost-effectiveness acceptability curve was generated to assess the likelihood that BIAsp30 would be considered value for money across a range of WTP thresholds (Figure 2). At a hypothetical WTP threshold of CNY 100,000, BIAsp30 had a 100% likelihood of being considered cost-effective from a third-party payer perspective.

Sensitivity Analyses

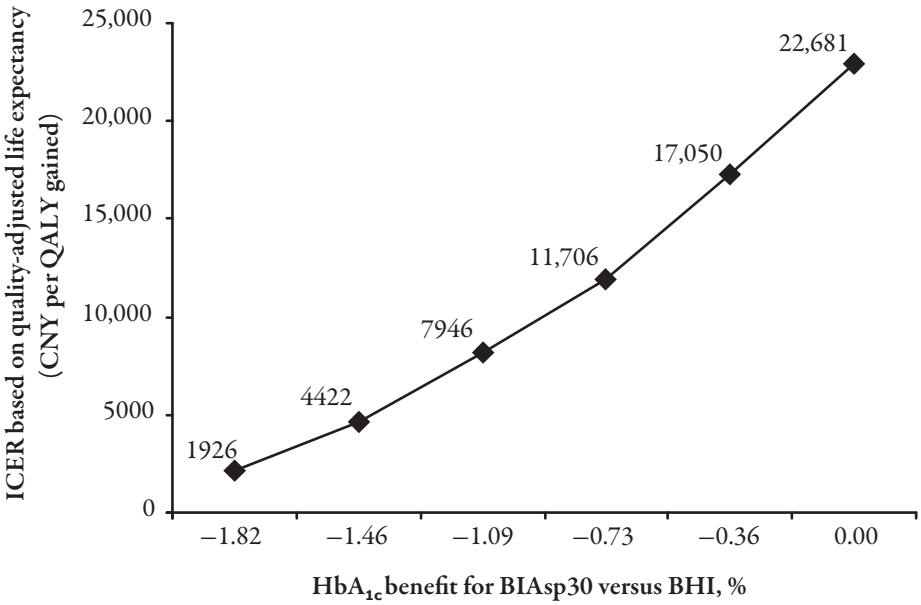
The results of a series of one-way sensitivity analyses revealed that modelled outcomes were most sensitive to changes

Table 7. Sensitivity analyses.

Sensitivity analysis	Quality-adjusted life expectancy (QALYs)			Direct costs (CNY)			ICER (CNY per QALY gained)
	BIAsp30	BHI	Difference	BIAsp30	BHI	Difference	
Base case (30-year time horizon)	*6.32 (0.12)*	*5.41 (0.11)*	*0.91*	*203,126 (4644)*	*201,376 (5252)*	*1751*	*1926*
10-year time horizon	4.42 (0.06)	3.89 (0.06)	0.53	126,194 (2537)	126,721 (2715)	−527	BIAsp30 dominant
20-year time horizon	6.01 (0.10)	5.18 (0.09)	0.83	187,672 (3949)	187,190 (4530)	481	583
Costs discounted at 6%, QALYs not discounted	8.20 (0.18)	6.95 (0.15)	1.25	157,492 (3251)	156,647 (3747)	845	679
Complication costs increased by 20%	6.32 (0.12)	5.41 (0.11)	0.91	232,729 (5465)	234,382 (6238)	−1652	BIAsp30 dominant
Complication costs decreased by 20%	6.32 (0.12)	5.41 (0.11)	0.91	178,489 (3918)	173,600 (4362)	4889	5377
No improvement in hypoglycaemic rates	5.75 (0.12)	5.41 (0.11)	0.34	206,764 (4724)	201,376 (5252)	5388	15,955

Values shown are means with standard deviations in parentheses.
QALY=quality-adjusted life year; CNY=Chinese Yuan; ICER=incremental cost-effectiveness ratio; BIAsp30=biphasic insulin aspart 30; BHI=biphasic human insulin.

Figure 3. Incremental cost-effectiveness ratios across a range of relative HbA_{1c} benefits for BIAsp30 versus BHI. BHI=biphasic human insulin; BIAsp30=biphasic insulin aspart 30; HbA_{1c}=glycosylated haemoglobin; ICER=incremental cost-effectiveness ratio; CNY=Chinese Yuan; QALY=quality-adjusted life year.



in treatment effects, time horizons and complication costs (Table 7). Varying the discount rates applied to future costs and clinical benefits had little effect on overall results. When the simulation was performed over a 10-year time horizon BIAsp30 was associated with improved quality-adjusted life expectancy of 0.53 QALYs and cost savings of CNY 527 per patient. When the simulation was performed over a 20-year time horizon, BIAsp30 was associated with an increase of 0.83 QALYs and increased costs of CNY 481 per patient.

When the diabetes-related complication and management costs applied in the model were increased by 20% from the base case, BIAsp30 was associated with cost savings of CNY 1652 per patient. When these costs were reduced by 20% from the base case, BIAsp30 was associated with increased direct costs of CNY 4889 per patient (versus CNY 1751 in the base case). When no reduction in hypoglycaemic events was modelled for BIAsp30, improvements in quality-adjusted life expectancy were lowered to 0.34 QALYs gained per patient (vs 0.91 QALYs in the base case); BIAsp30 was associated with increased incremental costs of CNY 5388 per patient versus BHI (compared with CNY 1751 in the base case).

When five sensitivity analyses were performed using a range of HbA_{1c} reductions for BIAsp30 (from the −1.82%-points reduction observed in PRESENT, to the 0% reduction calculated in a Cochrane review of randomised clinical trials of insulin analogues[26]), ICERs remained below the WTP threshold used in this analysis of CNY 100,000 per QALY gained

(Figure 3). When no reduction in HbA_{1c} was simulated for BIAsp30, an ICER of CNY 22,681 per QALY gained was calculated. In this conservative scenario, life expectancy was equal for both treatment arms at 9.53 years per patient, and no significant reductions in the incidences of most diabetes-related complications were projected for BIAsp30. The reduced incidence of hypoglycaemic events accounted for the projected improvement in quality-adjusted life expectancy of 0.57 QALYs per patient in this scenario (vs 0.91 QALYs in the base case).

DISCUSSION

We have identified that switching type 2 diabetes patients who are poorly controlled on BHI to BIAsp30 is likely to be cost-effective in the Chinese setting from a third-party payer perspective, based on the findings of PRESENT and our modelling analysis. Extensive sensitivity analyses support the findings that switching to BIAsp30 is likely to result in greater clinical benefits in terms of life expectancy and quality-adjusted life expectancy, and that BIAsp30 would remain cost-effective even when treatment-associated reductions in HbA_{1c} are reduced, or eliminated completely, due to significant reductions in hypoglycaemic events observed in PRESENT.

Sensitivity analyses revealed that final outcomes were most sensitive to treatment effects, time horizons and diabetes-related complication costs. While in most tested scenarios BIAsp30 was associated with marginally increased costs compared with BHI, when projections were made over 10 years BIAsp30 was associated with cost savings. Because the HbA_{1c}-driven survival benefit for BIAsp30 becomes more pronounced after 10 years, more patients in the BHI arm were projected to remain alive in this scenario relative to the base case. Thus the significantly greater hypoglycaemic event rate in the BHI arm, which remains constant in all years, combined with the cost of hypoglycaemia (CNY 144 per major event), contributed to cost savings in this modelled scenario.

This study is the first to compile nationwide cost data in China for the range of complications and management costs associated with diabetes. We tested the impact that complication costs had on final outcomes. Unsurprisingly, increasing complication and management cost inputs by 20% improved the economic case for BIAsp30, where it was associated with cost savings versus BHI of CNY 1652. While medical costs relating to the treatment of diabetes-related complications vary substantially across China, in the collection of data from two economically and demographically dissimilar cities, Beijing and Chengdu, we have attempted to address regional variation. The fragmented nature of China's economic development and healthcare provision and the likely variance in healthcare costs suggest that further research is required to comprehensively compile costs for the range of diabetes-related complications in China. While a separate study would be worthwhile, the data we compiled may well be relevant to future economic evaluations performed in China.

This is also the first study to apply the CORE Diabetes Model to the Chinese setting. A limitation of this approach is that the model uses risk equations derived from clinical trials and epidemiological studies conducted in predominantly white cohorts.[32] Barzi et al. reported that a modified Framingham cardiovascular risk equation with fewer variables may significantly overestimate the risk of cardiovascular events in Asian populations.[51] Therefore, in an exploratory sensitivity analysis using the CORE Diabetes Model we applied a multiplier of 0.36 to the baseline risk of myocardial infarction, congestive heart failure and angina. This relative risk was derived from data reported by Barzi et al., weighted by the sex breakdown in PRESENT. In this exploratory scenario undiscounted life expectancy was increased by a further 0.55 and 0.64 years compared with the base case in the BIAsp30 and BHI treatment arms, respectively. Improved life expectancy for all patients (but particularly those receiving BHI in this scenario) can be attributable to the reduced risk of cardiovascular events, which has a greater impact on patients with higher HbA_{1c}. One corollary of increased life expectancy in both treatment arms is that patients on BHI will be at risk of costly hypoglycaemic events for a longer duration, leading to projected cost savings for BIAsp30 of CNY 117 per patient in this scenario.

The diabetes simulation model used incorporates data from landmark clinical trials and epidemiological studies, such as the UKPDS and the Framingham Heart Study, and has been validated and applied to various ethnicities including Asian.[32,57] Due to the need to incorporate country-specific data wherever possible, we have used China-specific non-diabetes-related mortality and ESRD data, in addition to Chinese diabetes patient management practices and complication costs.

A limitation of this study is that the clinical effects of BIAsp30 are derived from a single-arm, pre- and post-observational study, and not from a randomised clinical trial. Despite this drawback, observational studies allow the incorporation of information derived from real-life situations rather than the controlled trial environment. In PRESENT, initiation and titration of BIAsp30 was entirely at the discretion of the treating physician, reflecting current diabetes treatment practices in China. The improvements in glycaemic control observed in PRESENT were accompanied by a small increase in insulin dosage, from 32.83 to 33.59 IU per day after switching to BIAsp30. Additionally, the impact of HbA_{1c} reductions on final outcomes were extensively tested, with BIAsp30 projected to be cost-effective over a range of HbA_{1c} reductions using a reasonable WTP threshold of CNY 100,000 per QALY gained, due to the significant reductions in hypoglycaemia observed in PRESENT.

The current analysis was performed from the perspective of a third-party payer and therefore did not investigate the effect of treatment on the indirect costs associated with lost productivity. Consequently, by not including the societal implications of treatment it is possible that the overall benefit of BIAsp30 treatment is underestimated in this analysis.

CONCLUSION

We have demonstrated that switching to BIAsp30 in poorly controlled type 2 diabetes patients receiving BHI is likely to improve long-term clinical outcomes and would be considered cost-effective in the Chinese setting, based on the findings of PRESENT and our modelling analysis. We do not claim that BIAsp30 is cost-effective compared to BHI in insulin-naïve or well-controlled type 2 diabetes patients.

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