Adv Ther (2012)
DOI 10.1007/s12325-012-0065-1

ORIGINAL RESEARCH

A UK Analysis of the Cost-Effectiveness of Humalog Mix75/25 and Mix50/50 Versus Long-Acting Basal Insulin

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Received: Oct 25, 2012 / Published online:

ABSTRACT

Introduction: As healthcare spending on diabetes and its complications continues to rise, the optimization of prescribed insulin regimens is becoming increasingly important from both clinical and economic perspectives. The aim of the present study was to evaluate the cost-effectiveness of 75/25 biphasic insulin lispro and 50/50 biphasic insulin lispro (Humalog® Mix75/25 and Humalog® Mix50/50, respectively; Eli Lilly and Company, Indianapolis, IN, USA) compared with a long-acting analog insulin regimen in patients with type 2 diabetes.

Methods: A published and validated computer simulation model of diabetes was used to evaluate the cost-effectiveness of 75/25 and 50/50 biphasic insulin lispro versus a long-acting analog insulin (insulin glargine) from the perspective of a healthcare payer in the UK. Treatment effects in terms of glycated hemoglobin (HbA_{1c}) benefits were taken from a recent meta-analysis. Direct medical costs including pharmacy, complication, and patient management costs were obtained from published sources. All costs were expressed in 2008 British pounds sterling (GBP), and future costs and clinical benefits were discounted at 3.5% per annum. Sensitivity analyses were performed.

Results: 75/25 and 50/50 biphasic insulin lispro were associated with improvements in life expectancy of 0.09 and 0.13 years, respectively, improvements in quality-adjusted life expectancy of 0.09 quality-adjusted life years (QALYs) and 0.12 QALYs, respectively, and reductions in cost of GBP 1,217 and GBP 430, respectively, when compared with long-acting analog insulin.

Conclusion: Based on a recently published meta-analysis, biphasic analog insulins are likely to improve clinical outcomes and reduce costs

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versus long-acting analog insulins in the long-term treatment of patients with type 2 diabetes in the UK.

Keywords: Biphasic insulin; Cost-effectiveness; Diabetes; Long-acting analog insulin; United Kingdom

INTRODUCTION

The prevalence and incidence of type 2 diabetes continues to increase in the UK. Between 1996 and 2005, González et al. estimated that the overall prevalence of diabetes (both type 1 and type 2) in the UK increased from 2.8% to 4.3% [1]. Over the same period, the incidence of type 2 diabetes increased by approximately 66%, from 2.60 to 4.31 cases per 1,000 person-years [1]. Furthermore, although it has long been observed that the prevalence and incidence of diabetes in the UK have been increasing, data suggest that the rate of increase has accelerated in recent years, driven in part by increasing levels of obesity [2]. As a natural corollary of this increased incidence and prevalence, the economic burden associated with managing patients with type 2 diabetes has also increased, leading to a heightened awareness among prescribers and healthcare payers of the need for cost-effective management of the condition.

Recently, the increase in economic burden associated with treating diabetes has been exacerbated by the integration of findings from recent studies into diabetes treatment guidelines. Specifically, studies such as Steno-2, the Collaborative Atorvastatin Diabetes Study (CARDS), the Hypertension Optimal Treatment (HOT) study and the Microalbuminuria, Cardiovascular, and Renal Outcomes substudy of the Heart Outcomes Prevention Evaluation (MICRO-HOPE), have indicated that a multifactorial approach to treatment including, for example, oral antidiabetics, antihypertensives, and statins, is beneficial in terms of reducing complications and controlling diabetes [3, 4, 5]. However, even with this multifaceted approach to treatment, the chronic and progressive nature of diabetes means that patients ultimately require insulin to maintain glycemic control. As such, it is unsurprising that the proportion of type 2 diabetes patients treated with insulin in the UK has remained relatively stable in recent years (15.1% in 1996 and 15.6% in 2005) [1, 6].

Although the proportion of diabetes patients receiving insulin has remained relatively constant, there has been a significant shift away from prescribing neutral protamine Hagedorn (NPH) insulin towards prescribing the newer human analog insulins that are produced synthetically using recombinant DNA [7]. Of the 5.7 million insulin prescriptions issued in the UK in 2009/10, 4.5 million prescriptions were for human analog insulins, representing 80.2% of all insulin prescriptions (compared with just 48.7% in 2004/05) [7]. In 2009/10, the net cost of all insulin prescriptions in the UK was 299.2 million British pounds sterling (GBP), of which GBP 118.9 million (39.7%) was attributable to nonbiphasic intermediate and long-acting insulins, and GBP 96.2 million (32.2%) was attributable to biphasic insulins [7]. Given this ongoing increase in prescriptions for analog insulins, we sought to compare the cost-effectiveness of a number of commonly used analog insulins in patients with type 2 diabetes in the UK. The primary analysis focused on the comparison of 75/25 biphasic insulin lispro and 50/50 biphasic insulin lispro (Humalog® Mix75/25 and Humalog® Mix50/50, respectively; Eli Lilly and Company, Indianapolis, IN, USA) with a long-acting analog insulin regimen (insulin glargine; Lantus®; Sanofi S.A., Paris, France). 75/25 biphasic

insulin lispro comprises a 75/25 mix of insulin lispro protamine suspension and insulin lispro injection, whereas 50/50 biphasic insulin lispro comprises the same basal and prandial insulin components but in a 50/50 mix.

COHORT AND METHODS

Model

The analysis was performed using the previously published and validated CORE Diabetes Model (CDM; IMS Health, Basel, Switzerland), a detailed overview of which is provided by Palmer et al. [8, 9]. In summary, the CDM is a non-product-specific diabetes policy analysis tool that simulates disease progression and takes into account intensive or conventional diabetes therapy, screening and treatment strategies for microvascular complications, end-stage complications, and multifactorial interventions. Structurally, the model is based on a series of interdependent submodels that simulate mortality and diabetes-related complications (angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular disease, diabetic retinopathy, macula edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer and amputation). Each submodel has a semi-Markov structure and uses time, state, time-in-state, and diabetes type-dependent probabilities derived from published sources. The memoryless properties of standard Markov models are overcome using Monte Carlo simulation with tracker variables, which also allows interconnectivity and interaction between the individual complication submodels. Economic and clinical data can be edited by the user, enabling the creation of country- or provider-specific versions of the model. The CDM allows inclusion of new data as they become available, as well as investigation of new hypotheses.

Simulation Cohort and Treatment Effects

For the base-case analysis, baseline cohort characteristics were derived from published sources to represent a "typical" insulin-using cohort in the UK. Data were sourced from the UK cohort of the INSulin Titration – GAining an understanding of the burden of Type 2 diabetes in Europe (INSTIGATE) study and supplemented with data from other published UK-specific sources where data from INSTIGATE were not available (Table 1) [10]. In cases where no UK-specific data were available (proportion of patients with gross proteinuria and proliferative diabetic retinopathy at baseline), US-centric or global data were used as a surrogate.

Treatment effects in the base case were taken from a systematic review and meta-analysis published by Qayyum et al. (Table 2) [11]. In this meta-analysis, the authors reported weighted mean differences in changes in postprandial glucose (PPG), fasting plasma glucose (FPG), and HbA_{1c} for long-acting analog insulin and premixed human insulin in comparison with three premixed analog insulins (75/25 and 50/50 biphasic insulin lispro and biphasic insulin aspart 70/30). The primary analysis was the comparison of 75/25 and 50/50 biphasic insulin lispro with long-acting analog insulin.

The meta-analysis by Qayyum et al. [11] also reported odds ratios for the incidence of hypoglycemia (classified as serious, mild, symptom only, and unclassified). However, because of the heterogeneous nature of hypoglycemia reporting in the studies included in the meta-analysis (and the lack of statistical significance in the odds ratios for severe hypoglycemia), only changes in HbA_{1c} were factored into the base-case analysis

(the CDM does not have the ability to model long-term risk based on PPG or FPG). A series of sensitivity analyses were performed to establish the impact of minor/mild hypoglycemia on cost-effectiveness outcomes.

Table 1 Baseline cohort demographics and characteristics

Characteristic	Value	Reference
Demographics and risk factors (mean [SD])		
Start age (years)	59.5 (11.5)	[10]
Duration of diabetes (years)	8.0 (5.9)	[10]
Males (%)	64	[10]
HbA_{1c} (%)	10.2 (1.7)	[10]
HbA_{1c} (mmol/mol)	88 (19)	[10]
SBP (mmHg)	140 (19.0)	[10]
Total cholesterol (mmol/L)	4.5 (1.1)	[10]
HDL cholesterol (mmol/L)	1.2 (0.5)	[10]
LDL cholesterol (mmol/L)	2.2 (0.9)	[10]
Triglycerides (mmol/L)	2.7 (1.7)	[27]
Body mass index (kg/m^2)	31.9 (6.6)	[10]
Smokers (%)	13.8	[27]
Cigarettes per day	13.49	[1]
Alcohol consumption (fluid ounces/week)	5.20	[2]
Ethnic group (%)		
White (Caucasian patients)	96.8	[10]
Black (African patients)	1.2	[10]
Asian/Pacific Islander (West Asian patients)	2	[10]
Baseline CVD complications (%)		
History of MI	9.9	[27]
History of stroke	4.3	[27]
History of CHF	4.7	[27]
Baseline renal complications (%)		
History of microalbuminuria	0.6	[3]
History of gross proteinuria	0.1	[4]
Baseline ocular complications (%)		
History of background diabetic retinopathy	15.9	[1]
History of proliferative diabetic retinopathy	1.8	[5]
History of severe vision loss	0	[6]
Baseline neuropathy, ulcer, and amputation (%)		
History of neuropathy[a]	9.1	[27]
History of amputation[a]	1.2	[27]

CHF congestive heart failure, *CVD* cardiovascular disease, *HbA_{1c}* glycated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MI* myocardial infarction, *SBP* systolic blood pressure

[a] As the foot ulcer submodel has a 1-month cycle length, baseline ulcer status has little impact on long-term end-stage complications (i.e., amputation)

Table 2 Treatment effects used in the base-case analysis [11]

Effect	Change from baseline HbA_{1c}, % (95% CI)
Long-acting analog insulin	0 (UKPDS outcomes model)
75/25 biphasic insulin lispro (vs. long-acting analog insulin)	−0.33 (−0.48 to −0.17)
50/50 biphasic insulin lispro (vs. long-acting analog insulin)	−0.40 (−0.65 to −0.15)

CI confidence interval, *HbA_{1c}* glycated hemoglobin, *UKPDS* United Kingdom Prospective Diabetes Study

Costs, Discounting, and Time Horizon

The analysis was performed from the perspective of a healthcare payer in the UK (i.e., the National Health Service). Direct medical costs including pharmacy costs, costs associated with diabetes-related complications, and concomitant patient management costs (e.g., aspirin, statins, and angiotensin-converting enzyme inhibitors) were obtained from published sources or provided by the study sponsor (Eli Lilly and Company, Indianapolis, IN, USA) [12, 13]. Where necessary, costs were inflated to 2008 GBP values using the consumer price index for all items, as published by the UK Office for National Statistics (Table 3) [14]. In the base-case analysis it was assumed that the cost of insulin glargine was representative of the cost of a long-acting analog insulin. It was also assumed that patients took an average of 40 IU per day, regardless of insulin regimen, in line with the defined daily dose published by the World Health Organization (WHO) for long-acting insulins and analogs [15]. Additionally, for the base-case analysis it was assumed that no patients were taking oral antidiabetic agents (OADs). Sensitivity analyses were performed to establish the effect of including concomitant medication costs on cost-effectiveness outcomes by varying treatment costs by ±10%.

The base-case analysis was run over a time horizon of 35 years to capture all relevant long-term complications and associated costs, and to assess their impact on life expectancy and quality-adjusted life expectancy (QALE). All future costs and clinical outcomes were discounted at a rate of 3.5% per annum in line with published guidance in the UK setting [16].

Sensitivity Analyses

To establish the key drivers of the results and assess the robustness of results of the base-case analyses, several sensitivity analyses were performed. The influence of time horizon on the outcomes projected by the model was investigated by running analyses over 5, 10, 20, and 30 years (from the 35-year base-case analysis). Similarly, the effect of discount rates on future costs and clinical outcomes were investigated through analyses in which they were set (symmetrically) to 0% and 6% per annum. As hypoglycemia rates were not included in either arm of the base-case analyses, sensitivity analyses were performed in which minor hypoglycemia rates in the long-acting basal analog arm were set to representative values from the Qayyum et al. [11] meta-analysis. Values in the 75/25 and 50/50 biphasic insulin lispro arm were then set to a value derived from these using the odds ratios presented in the Qayyum et al. [11] meta-analysis (1.83 [95% confidence interval (CI) 0.92–3.67] for long-acting analog insulin compared with premixed analog insulin). While minor hypoglycemic events were not assumed to incur any cost from the healthcare payer perspective, a disutility of –0.0033 was applied for each event [17]. In terms of clinical effects, another two sensitivity analyses were performed

Table 3 Direct medical costs associated with modeled diabetes complications (both in the year of the event and in subsequent years), treatment, concomitant medications, and screening

Complication	Cost (GBP)	Reference
Myocardial infarction, year of event	5,091	[12]
Myocardial infarction, each subsequent year	838	[12]
Angina, year of onset	2,641	[12]
Angina, each subsequent year	872	[12]
Congestive heart failure, year of onset	2,944	[12]
Congestive heart failure, each subsequent year	1,032	[12]
Stroke, year of event	3,114	[12]
Stroke, each subsequent year	589	[12]
Stroke, death within 30 days	3,928	[12]
Annual cost of peripheral vascular disease	2,713	[12]
Annual cost of hemodialysis	28,867	[12]
Annual cost of peritoneal dialysis	21,675	[12]
Kidney transplant, first year	22,696	[12]
Kidney transplant, each subsequent year	7,472	[12]
Major hypoglycemia	433	[12]
Ketoacidosis, event	943	[12]
Laser treatment	783	[12]
Cataract operation	1,804	[12]
Blindness, first year	1,012	[12]
Blindness, each subsequent year	327	[12]
Annual cost of neuropathy	1,104	[12]
Amputation, procedure	10,187	[12]
Amputation, prosthesis	648	[12]
Gangrene treatment	2,391	[12]
Infected foot ulcer	1,489	[12]
Uninfected foot ulcer	1,453	[12]
Insulin costs	**Cost per IU (GBP)**	**Annual cost (GBP)**
Long-acting analog insulin (Lantus®[a])	0.02326	339.83
75/25 biphasic insulin lispro	0.01807	264.05
50/50 biphasic insulin lispro	0.01807	264.05
Cost of concomitant medications and screening	**Annual cost (GBP)**	**Reference**
Aspirin (75 mg dispersible aspirin three-times daily, pack size 100)	10.51	[7]
Statins (40 mg simvastatin once daily, pack size 28)	17.60	[13]
ACE inhibitors (25 mg captopril three-times daily, pack size 100)	18.40	[13]
Microalbuminuria screening	37	[8]
Gross proteinuria screening	37	[12]
Eye screening	31	[12]
Nonstandard ulcer treat (regranex)	20	[12]

All costs are presented in 2008 GBP

ACE angiotensin converting enzyme, *GBP* pounds sterling, *IU* international units

[a] Lantus®, Sanofi-aventis US LLC, USA

in which the HbA_{1c} change was set to either end of the 95% CIs from the meta-analysis (from the mean HbA_{1c} change used in the base case).

The effect of over- or underestimating the unit costs of diabetes complications used in the analysis was evaluated in two sensitivity analyses, which increased and decreased the values used by 10% from the base-case costs. Pharmacy costs were not altered in these sensitivity analyses. However, two separate analyses were performed in which the pharmacy costs (excluding patient management such as aspirin and statins) in both arms were varied by ±10%. This was to establish the magnitude of the effect of variations in insulin pricing on model outcomes. All other costs remained the same as in the base case.

Finally, two sensitivity analyses were performed in which the QALE estimation method was switched to use the tariff-based United Kingdom Prospective Diabetes Study (UKPDS) tobit model or a multiple regression formula from the University of Michigan (based on the self-administered Quality of Well-Being [QWB-SA] instrument) [18, 19].

RESULTS

Based on the findings of the Qayyum et al. [11] meta-analysis, the present analysis found both 75/25 and 50/50 biphasic insulin lispro to be associated with improvements in life expectancy and QALE when compared with long-acting analog insulin (Table 4). Specifically, 75/25 and 50/50 biphasic insulin lispro were found to increase life expectancy by 0.09 and 0.13 years, respectively, relative to long-acting analog insulin, over a 35-year time horizon. In terms of QALE, 75/25 biphasic insulin lispro resulted in an increase of 0.09 quality-adjusted life years (QALYs) relative to long-acting analog insulin. The equivalent increase with 50/50 biphasic insulin lispro was 0.12 QALYs. In both primary comparisons, direct medical costs were lower in the 75/25 and 50/50 biphasic insulin lispro arm in comparison with the long-acting analog insulin arm over the 35-year time horizon (Table 5). In the 75/25 biphasic insulin lispro comparison, lower pharmacy costs were the biggest single driver of incremental costs, whereas reduced cardiovascular complication

Table 4 Long-term (35-year) clinical outcomes associated with the use of 75/25 biphasic insulin lispro and 50/50 biphasic insulin lispro versus long-acting analog insulin

	50/50 biphasic insulin lispro Mean (SD)	**Long-acting analog insulin Mean (SD)**	**Difference Mean (SD)**
Undiscounted life expectancy (years)	13.42 (0.26)	13.19 (0.25)	+0.23
Discounted life expectancy (years)	9.89 (0.16)	9.76 (0.16)	+0.13 (0.22)
Undiscounted QALE (QALYs)	9.02 (0.17)	8.83 (0.17)	+0.19
Discounted QALE (QALYs)	6.77 (0.11)	6.65 (0.11)	+0.12 (0.15)
	75/25 biphasic insulin lispro	**Long-acting analog insulin**	**Difference**
Undiscounted life expectancy (years)	13.35 (0.25)	13.19 (0.25)	+0.16
Discounted life expectancy (years)	9.86 (0.15)	9.76 (0.16)	+0.09 (0.21)
Undiscounted QALE (QALYs)	8.97 (0.17)	8.83 (0.17)	+0.14
Discounted QALE (QALYs)	6.73 (0.11)	6.65 (0.11)	+0.09 (0.14)

Future costs and clinical benefits were discounted at 3.5% per annum unless otherwise indicated
QALE quality-adjusted life expectancy, *QALY* quality-adjusted life year, *SD* standard deviation

costs were the key driver in cost differences between the 50/50 biphasic insulin lispro and long-acting analog insulin arms.

Evaluation of cost-effectiveness showed that both 75/25 and 50/50 biphasic insulin lispro would be dominant compared with long-acting analog insulin, with 75/25 and 50/50 biphasic insulin lispro treatment leading to reduced costs and improved life expectancy and QALE. Incremental cost-effectiveness scatter plots for the 75/25 and 50/50 biphasic insulin lispro comparisons are shown in Fig. 1 and Fig. 2, respectively. The scatter plots present the incremental costs versus incremental effectiveness (QALYs gained) for 75/25 and 50/50 biphasic insulin lispro versus long-acting analog insulin, and shows 1,000 mean values, each representing a cohort of 1,000 patients run through the model. Data from the scatter plots were then used to generate an acceptability curve, which showed that, at a willingness-to-pay threshold of GBP 30,000 per QALY gained, there was an 84% probability that both 75/25 and 50/50 biphasic insulin lispro would be considered cost-effective in comparison with long-acting analog insulins.

Sensitivity Analyses

Sensitivity analyses were performed to assess the robustness of the base-case findings and determine the key drivers of the results. For both the 75/25 and 50/50 biphasic insulin lispro comparisons, the only scenario in which biphasic insulin lispro was not dominant was a scenario in which the incidence of mild hypoglycemia was altered (Tables 6 and 7). Using the mean and upper limit of the 95% CIs for the odds ratio of mild hypoglycemic events for 75/25 and 50/50 biphasic insulin lispro treatment arms versus long-acting analog insulin (1.83 and 3.67 for 75/25 and 50/50 biphasic insulin lispro, respectively) negated the incremental benefit in QALE observed with biphasic insulin lispro. However, using the lower bound of the 95% confidence interval (0.92) led to an increased incremental effectiveness in comparison with the base case (0.10 QALYs compared with 0.09

Table 5 Direct costs over patient lifetimes associated with 75/25 biphasic insulin lispro and 50/50 biphasic insulin lispro versus long-acting analog insulin

	Cost (2008 GBP)					
	75/25 biphasic insulin lispro	**Long-acting analog insulin**	**Difference**	**50/50 biphasic insulin lispro**	**Long-acting analog insulin**	**Difference**
Treatment	2,768	3,533	−765	2,778	2,658	120
Other management	620	615	5	623	615	8
Complications	**14,763**	**15,221**	**−458**	**14,663**	**15,221**	**−558**
Cardiovascular	7,256	7,427	−171	7,211	7,427	−216
Renal	901	1,038	−137	875	1,038	−163
Ulcer, amputation and, neuropathy	5,855	5,983	−128	5,836	5,983	−147
Eye	751	773	−22	741	773	−32
Hypoglycemia	0	0	0	0	0	0
Total	**18,152**	**19,369**	**−1,217**	**18,064**	**18,494**	**−430**

GBP British pounds sterling

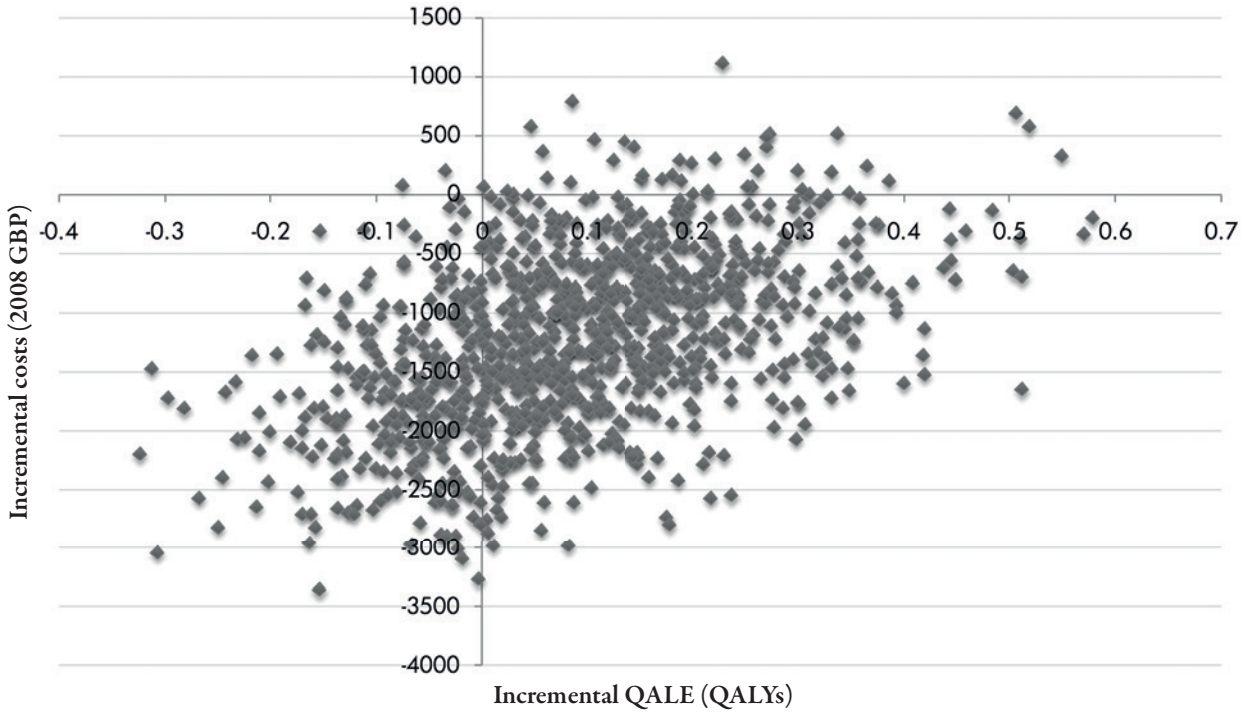

Fig. 1 Scatter plot of incremental costs versus incremental effectiveness of 75/25 biphasic insulin lispro versus a long-acting analog insulin. *GBP* British pounds sterling, *QALE* quality-adjusted life expectancy, *QALYs* quality-adjusted life years

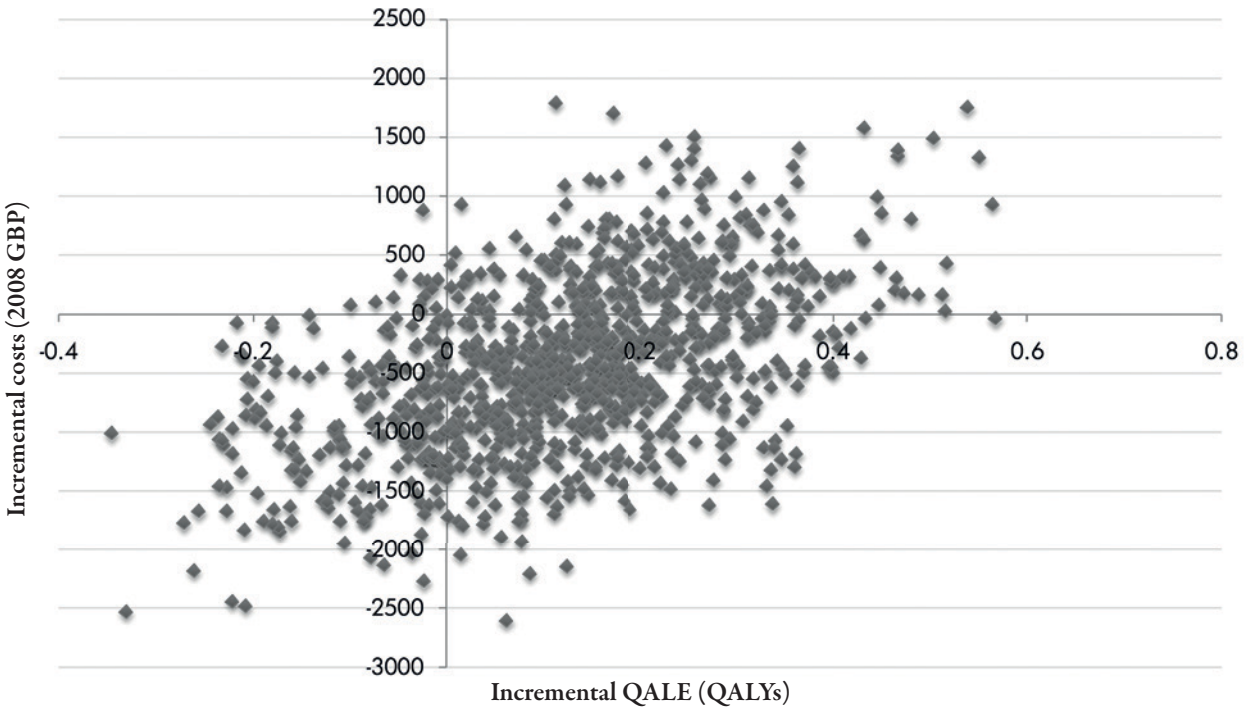

Fig. 2 Scatterplot of incremental costs versus incremental effectiveness of 50/50 biphasic insulin lispro versus long-acting analog insulin. *GBP* British pounds sterling, *QALE* quality-adjusted life expectancy, *QALYs* quality-adjusted life years

Table 6 Results of sensitivity analyses comparing 75/25 biphasic insulin lispro with long-acting analog insulin *(continued on next page)*

Analysis	QALE (QALYs)			Direct costs (GBP)			ICER (GBP per QALY gained)
	75/25 biphasic insulin lispro	LAAI	Difference	75/25 biphasic insulin lispro	LAAI	Difference	
Base case	**6.73 (0.11)**	**6.65 (0.11)**	**0.09 (0.14)**	**18,152 (540)**	**19,369 (549)**	**−1,217 (748)**	**75/25 biphasic insulin lispro dominant**
Highest OR of mild hypoglycemia	6.16 (0.10)	6.49 (0.11)	−0.32 (0.14)	18,152 (540)	19,369 (549)	−1,217 (748)	75/25 biphasic insulin lispro less costly, less effective
Lowest OR of mild hypoglycemia	6.59 (0.11)	6.49 (0.105)	0.10 (0.14)	18,152 (540)	19,369 (549)	−1,217 (748)	75/25 biphasic insulin lispro dominant
Mean OR of mild hypoglycemia	6.45 (0.10)	6.49 (0.105)	−0.04 (0.14)	18,152 (540)	19,369 (549)	−1,217 (748)	75/25 biphasic insulin lispro less costly, less effective
"Worst case" HbA_{1c}	6.69 (0.11)	6.65 (0.107)	0.05 (0.14)	18,333 (547)	19,369 (549)	−1,036 (720)	75/25 biphasic insulin lispro dominant
"Best case" HbA_{1c}	6.78 (0.11)	6.65 (0.107)	0.13 (0.15)	17,899 (550)	19,369 (549)	−1,470 (747)	75/25 biphasic insulin lispro dominant
5-year time horizon	3.02 (0.03)	3.00 (0.028)	0.02 (0.04)	4,388 (120)	4,853 (127)	−465 (164)	75/25 biphasic insulin lispro dominant
10-year time horizon	4.93 (0.06)	4.90 (0.056)	0.04 (0.08)	9,240 (257)	10,096 (264)	−855 (352)	75/25 biphasic insulin lispro dominant
20-year time horizon	6.48 (0.10)	6.41 (0.090)	0.07 (0.13)	16,016 (456)	17,257 (486)	−1,241 (631)	75/25 biphasic insulin lispro dominant
30-year time horizon	6.72 (0.10)	6.64 (0.105)	0.09 (0.14)	17,932 (531)	19,204 (567)	−1,272 (748)	75/25 biphasic insulin lispro dominant
University of Michigan QALE	5.79 (0.09)	5.72 (0.090)	0.07 (0.12)	18,152 (540)	19,369 (549)	−1,217 (748)	75/25 biphasic insulin lispro dominant
UKPDS tobit tariff QALE	8.15 (0.13)	8.06 (0.132)	0.09 (0.18)	18,152 (540)	19,369 (549)	−1,217 (748)	75/25 biphasic insulin lispro dominant

Table 6 continued

Analysis	QALE (QALYs)			Direct costs (GBP)			ICER (GBP per QALY gained)
	75/25 biphasic insulin lispro	LAAI	Difference	75/25 biphasic insulin lispro	LAAI	Difference	
0% discount rate	8.97 (0.17)	8.83 (0.168)	0.14 (0.23)	27,672 (960)	29,319 (970)	−1,647 (1,329)	75/25 biphasic insulin lispro dominant
6% discount rate	5.66 (0.08)	5.59 (0.082)	0.07 (0.11)	14,042 (388)	15,048 (394)	−1,006 (535)	75/25 biphasic insulin lispro dominant
10% increase in diabetes complication costs	6.73 (0.11)	6.65 (0.107)	0.09 (0.14)	19,628 (592)	20,891 (600)	−1,263 (819)	75/25 biphasic insulin lispro dominant
10% decrease in diabetes complication costs	6.73 (0.11)	6.65 (0.107)	0.09 (0.14)	16,675 (489)	17,847 (498)	−1,172 (678)	75/25 biphasic insulin lispro dominant

HbA_{1c} glycated hemoglobin, *GBP* British pounds sterling, *ICER* incremental cost-effectiveness ratio, *LAAI* long-acting analog insulin, *OR* odds ratio, *QALE* quality-adjusted life expectancy, *QALY* quality-adjusted life year, *UKPDS* United Kingdom Prospective Diabetes Study

QALYs in the base case) in the 75/25 biphasic insulin lispro versus long-acting analog insulin comparison. Similarly, in the 50/50 biphasic insulin lispro versus long-acting analog insulin comparison the corresponding improvements were 0.18 and 0.32 QALYs, respectively, versus 0.12 QALYs in the base case.

Sensitivity analyses were also performed around the HbA_{1c} benefit associated with 75/25 and 50/50 biphasic insulin lispro. Specifically, the HbA_{1c} change was varied between the upper and lower bounds of the 95% CIs reported by Qayyum et al. [11]. However, in all HbA_{1c} scenarios included in the current analysis, 75/25 biphasic insulin lispro remained dominant over long-acting analog insulin, with benefits in QALE ranging from 0.05 to 0.13 QALYs for 75/25 biphasic insulin lispro versus long-acting analog insulin. For the 50/50 biphasic insulin lispro comparison, the HbA_{1c} worst case scenario reduced the QALE benefit to 0.04 QALYs and reduced cost savings to GBP 124 versus long-acting analog insulin.

Several sensitivity analyses were run in which the time horizon was shortened relative to the base-case analysis. Performing the analyses over shorter time horizons reduced the cost-savings and effectiveness benefits observed with both 75/25 and 50/50 biphasic insulin lispro versus long-acting analog insulin, but both 75/25 and 50/50 biphasic insulin lispro remained dominant in all scenarios tested. Increasing the time horizon of the simulations led to greater cost savings in the 75/25 and 50/50 biphasic insulin lispro treatment arms, primarily because of a reduction in the number of end-stage complications with the treatment versus long-acting analog insulin.

The impact of using different methods of QALE estimation was also investigated. Using either the method proposed by the University of Michigan or the UKPDS tariff-based tobit model

Table 7 Results of sensitivity analyses comparing 50/50 biphasic insulin lispro with long-acting analog insulin *(continued on next page)*

Analysis	QALE (QALYs)			Direct costs (GBP)			ICER (GBP per QALY gained)
	50/50 biphasic insulin lispro	LAAI	Difference	50/50 biphasic insulin lispro	LAAI	Difference	
Base case	**6.77 (0.11)**	**6.65 (0.11)**	**0.12 (0.15)**	**18,064 (549)**	**18,494 (541)**	**−430 (720)**	**50/50 biphasic insulin lispro dominant**
Highest OR of mild hypoglycemia	6.19 (0.10)	6.30 (0.10)	−0.11 (0.14)	18,064 (549)	18,494 (541)	−430 (720)	50/50 biphasic insulin lispro less costly, less effective
Lowest OR of mild hypoglycemia	6.62 (0.11)	6.30 (0.10)	0.32 (0.15)	18,064 (549)	18,494 (541)	−430 (720)	50/50 biphasic insulin lispro dominant
Mean OR of mild hypoglycemia	6.48 (0.11)	6.30 (0.10)	0.18 (0.15)	18,064 (549)	18,494 (541)	−430 (720)	50/50 biphasic insulin lispro dominant
"Worst case" HbA_{1c}	6.69 (0.11)	6.65 (0.11)	0.04 (0.13)	18,371 (576)	18,494 (541)	−124 (716)	50/50 biphasic insulin lispro dominant
"Best case" HbA_{1c}	6.82 (0.11)	6.65 (0.11)	0.17 (0.15)	17,665 (517)	18,494 (541)	−829 (735)	50/50 biphasic insulin lispro dominant
5-year time horizon	3.02 (0.03)	3.00 (0.03)	0.02 (0.04)	4,357 (122)	4,494 (126)	−137 (168)	50/50 biphasic insulin lispro dominant
10-year time horizon	4.94 (0.05)	4.90 (0.06)	0.05 (0.07)	9,180 (254)	9,488 (262)	−308 (349)	50/50 biphasic insulin lispro dominant
20-year time horizon	6.50 (0.10)	6.41 (0.09)	0.09 (0.13)	15,907 (460)	16,424 (481)	−517 (644)	50/50 biphasic insulin lispro dominant
30-year time horizon	6.73 (0.11)	6.64 (0.11)	0.10 (0.15)	17,833 (548)	18,332 (559)	−499 (768)	50/50 biphasic insulin lispro dominant
University of Michigan QALE	5.82 (0.09)	5.72 (0.09)	0.10 (0.13)	18,064 (549)	18,494 (541)	−430 (720)	50/50 biphasic insulin lispro dominant
UKPDS tobit tariff QALE	8.18 (0.14)	8.06 (0.13)	0.12 (0.19)	18,064 (549)	18,494 (541)	−430 (720)	50/50 biphasic insulin lispro dominant

Table 7 continued

Analysis	QALE (QALYs)			Direct costs (GBP)			ICER (GBP per QALY gained)
	50/50 biphasic insulin lispro	LAAI	Difference	50/50 biphasic insulin lispro	LAAI	Difference	
0% discount rate	9.02 (0.17)	8.83 (0.17)	0.19 (0.24)	27,591 (976)	28,126 (955)	−535 (1,295)	50/50 biphasic insulin lispro dominant
6% discount rate	5.68 (0.09)	5.59 (0.08)	0.09 (0.12)	13,961 (392)	14,323 (389)	−363 (513)	50/50 biphasic insulin lispro dominant
10% increase in diabetes complication costs	6.77 (0.11)	6.65 (0.11)	0.12 (0.15)	19,531 (601)	20,016 (592)	−486 (788)	50/50 biphasic insulin lispro dominant
10% decrease in diabetes complication costs	6.77 (0.11)	6.65 (0.11)	0.12 (0.15)	16,598 (497)	16,972 (490)	−374 (652)	50/50 biphasic insulin lispro dominant

HbA_{1c} glycated hemoglobin, *GBP* British pounds sterling, *ICER* incremental cost-effectiveness ratio, *LAAI* long-acting analog insulin, *OR* odds ratio, *QALE* quality-adjusted life expectancy, *QALY* quality-adjusted life year, *UKPDS* United Kingdom Prospective Diabetes Study

resulted in a decrease in the incremental benefit in QALE observed with 50/50 biphasic insulin lispro. In these analyses, the benefit was reduced to 0.10 QALYs and 0.12 QALYs for the University of Michigan method and the UKPDS method, respectively. In the 75/25 biphasic insulin lispro comparison, the University of Michigan method reduced the incremental benefit to 0.07 QALYs (vs. 0.09 QALYs in the base case), while using the UKPDS method led to a comparable incremental benefit of 0.09 QALYs versus long-acting analog insulin.

DISCUSSION

Based on HbA_{1c} change data published by Qayyum et al., [11] the present analysis indicated that, in the UK setting, 75/25 and 50/50 biphasic insulin lispro are likely to be cost saving and associated with improved clinical outcomes in comparison with long-acting analog insulin. A series of one-way sensitivity analyses showed that the base-case results were largely insensitive to changes in a number of the key modeling assumptions. However, changes in assumptions regarding the incidence of minor hypoglycemic events had a considerable impact on patients' quality of life (QOL) (and consequently QALE) in the analysis. Notably, in scenarios that used the mean and upper limits of the odds ratios for mild hypoglycemic events for 75/25 and 50/50 biphasic insulin lispro versus long-acting analog insulin, the QOL benefits observed in the base-case analyses were negated and 75/25 and 50/50 biphasic insulin lispro were no longer dominant to long-acting analog insulin.

In terms of the magnitude of effects observed in the study, the increases in QALE of 0.09 and 0.12 QALYS with 75/25 and 50/50 biphasic insulin lispro, respectively, fall within the range of previous cost-effectiveness analyses reporting head-to-head comparisons of insulin regimens.

For instance, a 2006 study comparing the cost-effectiveness of insulin detemir with insulin glargine reported an increase in QALE of 0.06 QALYs over a lifetime time horizon [20], while a 2007 study comparing biphasic insulin aspart 70/30 with insulin glargine reported an increase of 0.19 QALYs over a 35-year time horizon [21]. While the cost savings associated with 75/25 and 50/50 biphasic insulin lispro were relatively modest in the present analysis, we note that they compare favorably with the cost increases reported in these previous comparisons of insulin regimens.

The current study has a number of limitations that should be acknowledged. Firstly, incidence of hypoglycemia was excluded from the base-case analysis. The rationale for this omission was the nature and quality of data presented in the Qayyum et al. [11] meta-analysis. Notably, the analysis only presented aggregate data for all premixed analog insulins including, for example, biphasic insulin aspart as well as 75/25 and 50/50 biphasic insulin lispro. More importantly, the analysis only examined the incidence of hypoglycemia in a small number of studies, which (as Qayyum and colleagues noted [11]) exhibited considerabe heterogeneity in terms of their definitions and reporting of hypoglycemia. Indeed, a number of the studies were not statistically powered to detect differences in hypoglycemic event rates. This high prevalence of heterogeneity in hypoglycemia reporting has also been acknowledged by other study authors. For example, in a recent meta-analysis designed to determine optimal insulin regimens, Lasserson et al. noted that it was not possible to perform a pooled analysis of hypoglycemia rates because of variations in definitions and underreporting of measures of dispersion [22].

A second limitation that should be noted is the use of data from a meta-analysis of short-term clinical data to make long-term projections. The aim of the present study was to generate a realistic estimate of the long-term value of patients taking 75/25 and 50/50 biphasic insulin lispro versus long-acting analog insulin. To this end, we believe the Qayyum et al. [11] meta-analysis represents the most comprehensive review of the relative effectiveness of these modern analog insulins. In terms of the uncertainty around making long-term projections from short-term data, this remains one of the essential tenets of much health economic modeling and, in the absence of long-term clinical trial data, represents the best available option for health economists.

One final potential criticism of the present study lies in the simulation cohort, which was based primarily on the UK cohort from the INSTIGATE study, a prospective, multi-country, observational analysis designed to examine clinical practice and outcomes in patients initiating insulin in five European countries. All patients enrolled in INSTIGATE were therefore insulin-naïve at baseline. Of the 45 studies included in the Qayyum et al. [11] meta-analysis, only 10 trials were conducted exclusively in insulin naïve patients (compared with 25 studies exclusively in insulin-treated patients, one study that enrolled a mix, and nine in which the history of insulin treatment was not specified). However, the sensitivity analyses in which the modeled HbA_{1c} benefit was set to either boundary of the 95% CIs showed that 75/25 and 50/50 biphasic insulin lispro maintained dominance over long-acting analog insulin, suggesting that the fundamental findings of the present study would likely remain unchanged in cohorts with differing histories of diabetes medication use.

In terms of the applicability of the present study, it is important to consider where the basal insulin analogs and premixed insulin formulations are used in the treatment of

type 2 diabetes. The American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus algorithm for the management of hyperglycemia in type 2 diabetes recommends initiating insulin with intermediate- or long-acting insulins only when patients have failed to achieve or sustain glycemic goals after lifestyle intervention plus one or two OADs (typically metformin followed by the addition of sulfonylurea) [23]. While the ADA/EASD statement does not make specific recommendations with regard to the initial choice of insulin, guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend that NPH insulin is used unless the patient has difficulty injecting, would need to take NPH twice daily in combination with OADs, or experiences recurrent hypoglycemic episodes on NPH insulin [24]. Subsequent studies have reported that the choice of NPH as a starter insulin may result in significant cost savings relative to insulin analogs [25, 26]. The present study therefore provides payers and prescribers with the health economic evidence to select an insulin regimen in patients who would benefit from switching away from NPH.

In conclusion, the results of the primary analyses presented here suggest that, from the perspective of a healthcare payer in the UK, biphasic insulin lispro 75/25 and 50/50 represent dominant treatment options when compared with long-acting analog insulins for the treatment of patients with type 2 diabetes.

ACKNOWLEDGMENTS

This study was supported by a grant from Eli Lilly and Company. Dr. Valentine is the guarantor for this article, and takes responsibility for the integrity of the work as a whole.

Conflict of interest. Bradley H. Curtis is a full-time employee of Eli Lilly and Company. Richard F. Pollock, Jayne Smith-Palmer, and William J. Valentine are full-time employees of Ossian Health Economics and Communications GmbH, which has received consulting fees from Eli Lilly and Company.

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