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ORIGINAL RESEARCH ARTICLE

Treating Type 1 Diabetes Mellitus with a Rapid-Acting Analog Insulin Regimen vs. Regular Human Insulin in Germany: A Long-Term Cost-Effectiveness Evaluation

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Abstract

Objective The aim of the present study was to evaluate the cost effectiveness of rapid-acting analog insulin relative to regular human insulin in adults with type 1 diabetes mellitus in Germany.

Methods The PRIME Diabetes Model, a patient-level, discrete event simulation model, was used to project long-term clinical and cost outcomes for patients with type 1 diabetes from the perspective of a German healthcare payer. Simulated patients had a mean age of 21.5 years, duration of diabetes of 8.6 years, and baseline glycosylated hemoglobin of 7.39%. Regular human insulin and rapid-acting analog insulin regimens reduced glycosylated hemoglobin by 0.312 and 0.402%, respectively. Compared with human insulin, hypoglycemia rate ratios with rapid-acting analog insulin were 0.51 (non-severe nocturnal) and 0.80 (severe). No differences in non-severe diurnal hypoglycemia were modeled. Discount rates of 3% were applied to future costs and clinical benefits accrued over the 50-year time horizon.

Results In the base-case analysis, rapid-acting analog insulin was associated with an improvement in quality-adjusted life expectancy of 1.01 quality-adjusted life-years per patient (12.54 vs. 11.53 quality-adjusted life-years). Rapid-acting analog insulin was also associated with an increase in direct costs of €4490, resulting in an incremental cost-effectiveness ratio of €4427 per quality-adjusted life-year gained vs. human insulin. Sensitivity analyses showed that the base case was driven predominantly by differences in hypoglycemia; abolishing these differences reduced incremental quality-adjusted life expectancy to 0.07 quality-adjusted life-years, yielding an incremental cost-effectiveness ratio of €74,622 per quality-adjusted life-year gained.

Conclusions Rapid-acting analog insulin is associated with beneficial outcomes in patients with type 1 diabetes and is likely to be considered cost effective in the German setting vs. regular human insulin.

Key Points for Decision Makers

Based on the modeling analysis, rapid-acting analog insulin would be considered cost effective relative to regular human insulin in adult patients with type 1 diabetes mellitus in Germany.

The cost utility of rapid-acting human insulin was driven primarily by reductions in non-severe nocturnal, and severe hypoglycemic events, although some benefit was also derived from improved glycemic control.

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1 Introduction

Type 1 diabetes mellitus represents a substantial clinical and economic burden for the German healthcare system. International Diabetes Federation estimates indicated that the incidence rate of type 1 diabetes is approximately 21.9 per 100,000 of the population in children aged up to 14 years [1]. A 2013 study has indicated that annual healthcare costs are approximately €3745 (inter-quartile range: €1943–€4881) per patient in the pediatric population [2]. Earlier estimates suggest that annual costs are likely to be higher amongst adults and increase substantially when patients experience complications [3, 4]. Optimizing therapy and the use of healthcare resources may be of particular importance in type 1 diabetes as incidence rates are increasing in Europe and worldwide, particularly in children under 5 years of age where the incidence has been projected to double between 2003 and 2020 [1, 5, 6].

Reimbursement of insulin analogs has been a controversial issue in Germany for some time. Insulin analogs are designed to offer an insulin replacement strategy that more closely imitates normal human physiology (traditionally assumed as ~ 50% basal insulin secretion throughout the day and ~ 50% prandial secretion in response to meals) [7]. Analog insulin preparations became available on the US market with the approval of insulin lispro (Eli Lilly and Company) in 1996 [7]. However, analog insulin preparations are associated with higher acquisition costs than human insulin and evidence supporting their clinical benefits beyond reductions in hypoglycemia, particularly in type 2 diabetes, has been mixed [7]. Following an earlier decision to exclude insulin analogs from the treatment of type 2 diabetes in Germany, the Federal Joint Committee (G-BA) issued an edict to similarly preclude insulin analogs from therapy for type 1 diabetes in 2008 and worldwide controversy ensued [8]. For instance, the IDF expressed "major concern about the potential discontinuation of reimbursement for short-acting insulin analogs to people with type 1 diabetes in Germany, which would result in many patients being excluded from this type of therapy" [7]. This decision was eventually withdrawn but the situation demonstrated the difficulty in objectively assessing the costs and cost effectiveness of analog vs. human insulin therapy.

Given this background, regular evaluation of the cost effectiveness of hypoglycemic agents, not only rapid-acting insulin analogs, is crucial in terms of optimizing healthcare delivery [9, 10]. Not only should these analyses be based on the best available clinical data and up-to-date costs, but the choice of diabetes model is likely to also play an important role in generating the most appropriate evidence to support decision making. Many of the commonly used models of type 1 diabetes were developed more than a decade ago [11, 12]. This issue may be compounded by the fact that many historical models of type 1 diabetes have also relied on data from patients with type 2 diabetes or from the general population, which may not appropriately reflect risk in a population with type 1 diabetes [13, 14]. The aim of the present study was to provide an up-to-date evaluation of the cost effectiveness of rapid-acting insulin analogs compared with regular human insulin in adults with type 1 diabetes in Germany, using a newly developed and validated model using data exclusively from populations with type 1 diabetes to estimate complication risk.

2 Methods

2.1 PRIME Diabetes Model

The PRIME Diabetes Model was developed to estimate the risk of complications, costs, life expectancy, and quality-adjusted life expectancy in patients with type 1 diabetes in a transparent and treatment-independent manner based on the most recent data specific to patients with type 1 diabetes. The PRIME Diabetes Model has been described elsewhere in the literature and is freely accessible over the Internet for academic research [15, 16]. In brief, the model is a modular, patient-level, discrete event simulation model programmed in Java and designed to allow for easy and transparent projection of clinical and health economic outcomes. The model incorporates clinical data taken exclusively from large-scale trials and database analyses of patients with type 1 diabetes; unlike other patient-level models of type 1 diabetes, the PRIME Diabetes Model does not make use of surrogate or proxy data from general patient populations or from patients with type 2 diabetes. The PRIME Diabetes Model also makes use of model averaging and multi-models (i.e., the combination of outputs from multiple published risk models using model weights derived from multivariate divergence analysis of the analysis cohort and the risk model derivation cohort) to incorporate as much available clinical type 1 diabetes data as possible.

The PRIME Diabetes Model also includes covariance of patient characteristics and risk factor progression based on an analysis of patient-level data from patients enrolled in the Diabetes Control and Complications Trial (DCCT). Sampling from distributions around all model inputs and risk model parameters allows for comprehensive probabilistic sensitivity analysis to be performed [16]. Model outputs include undiscounted and discounted life expectancy, costs, and quality-adjusted life expectancy, evolution of risk factors such as glycosylated hemoglobin (HbA_{1c}) and systolic blood pressure, the cumulative

incidence of complications over time, and an incremental cost-effectiveness ratio (ICER). The PRIME Diabetes Model can be accessed online at https://prime-diabetes-model.com, is free for academic use, has been independently validated and a full description is provided in Valentine et al. [15–17].

2.2 Evidence Review

A structured literature search of PubMed, EMBASE, and the Cochrane Library was undertaken to identify clinical trials and meta-analyses published between 1 January, 2006 and 1 January, 2015 and provide data specific to the use of rapid-acting analog insulin vs. regular human insulin in patients with type 1 diabetes. The selection of the 2006 threshold was chosen to exclude trial data and meta-analyses that may not represent modern routine clinical practice in terms of treatment of type 1 diabetes, e.g., studies predating the widespread use of continuous glucose monitoring and flexible intensive insulin therapy through programs such as Dose Adjustment For Normal Eating [18]. The search strategies for identifying clinical trials and meta-analyses in PubMed are included in Tables 1 and 2 of the Electronic Supplementary Material (ESM). Data from the articles included after abstract screening and the full-text review were used to inform the modeling analysis.

2.3 Model Population

The literature review identified two studies that provided sufficient detail on German type 1 diabetes populations to define most of the mean baseline cohort characteristics along with measures of variance around continuous variables (Table 1) [19, 20]. Neither of the identified trials provided data on body mass index and these values were therefore taken from a comparable European cohort, which was well matched for age and duration of diabetes [21]. A simulated cohort of 100,000 patients was used for all modeled analyses. German life tables from the World Health Organization were employed to estimate the risk of mortality not explicitly captured by complication-specific submodels [22]. Life tables were indexed by sex and age and, to eliminate overestimation of overall mortality, were calibrated by running the PRIME Diabetes Model with background mortality disabled and subtracting the aggregated modeled complication-specific mortality risk estimates from the published estimates.

2.4 Risk Factors and Insulin Use

The PRIME Diabetes Model is capable of modeling treatment-induced changes in HbA_{1c}, body mass index, cholesterol, systolic blood pressure, and hypoglycemia and ketoacidosis rates. The meta-analyses and clinical trials identified in the literature search reported that rapid-acting analog insulin lowered HbA_{1c} and the rates of severe and nocturnal hypoglycemia compared with regular human insulin (Table 2) [21, 23–26]. The Singh et al. meta-analysis was selected as the basis for modeling differences in HbA_{1c}, nocturnal hypoglycemia, and severe hypoglycemia on the grounds that it included the largest sample size both in terms of included trials (22, 10, and 4 trials for HbA_{1c}, severe hypoglycemia, and nocturnal hypoglycemia, respectively) and patients enrolled (n = 6021, 4502, and 725 patients, respectively) [24].

Subsequent meta-analyses included fewer patients (as a result of, for example, stipulating the use of a specific basal insulin in the inclusion criteria), included a mixture of patients with type 1 and type 2 diabetes, and/or focused on specific patient sub-groups (e.g., pregnant women) [27–30]. One clinical trial reported that rapid-acting analog insulin increased the rate of non-severe daytime hypoglycemia compared with regular human insulin [31]. As the difference was not reported as significant, it was excluded

Table 1 Mean baseline characteristics of the type 1 diabetes mellitus population

Characteristic	Mean	Standard deviation	Source
Age (years)	21.5	14.9	Raile et al. [19]
Duration of diabetes (years)	8.6	9.0	Raile et al. [19]
Male (%)	52.6	NA	Raile et al. [19]
HbA_{1c} (%)	7.98	1.7	Raile et al. [19]
BMI (kg/m^2)	23.75	2.55	Brunetti et al. [21]
SBP (mmHg)	119.7	15.1	Raile et al. [19]
Total cholesterol (mmol/L)	5.03	1.48	Hammes et al. [20]
HDL cholesterol (mmol/L)	1.66	0.47	Hammes et al. [20]
LDL cholesterol (mmol/L)	2.63	0.63	Hammes et al. [20]
Smoker (%)	29.5	NA	Hammes et al. [20]

BMI body mass index, *HbA_{1c}* glycosylated hemoglobin, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *SBP* systolic blood pressure

Table 2 Resource use and clinical effects associated with rapid-acting analog insulin (RAAI) and regular human insulin (RHI) regimens

Parameter	RHI	RAAI	Difference	Source
Insulin use				
Basal insulin, IU/day (SD)	16.4 (5.9)	19.3 (6.5)	+ 2.9	[21]
Bolus insulin, IU/day (SD)	22.4 (7.3)	27.2 (12.2)	+ 4.8	[21]
Total cost, € per year (2015)	488.72	713.35	+ 224.64	
Treatment effects				
HbA_{1c} (%)	− 0.312	− 0.402	− 0.09 (95% CI − 0.16 to − 0.02)	[21, 24]
Daytime non-severe hypoglycemia (events per patient-year)	66.23[a]	66.23	RR 1.00[b]	[23, 26, 31]
Nocturnal non-severe hypoglycemia (events per patient-year)	16.77[a]	8.551	RR 0.51 (95% CI 0.42–0.62)	[23, 24, 31]
Severe hypoglycemia (events per patient-year)	0.2	0.16	Relative risk 0.80 (95% CI 0.67–0.96)	[23–25]

Differences in HbA_{1c}, nocturnal severe hypoglycemia, and severe hypoglycemia rates were based on Singh et al. [24]. The reference HbA_{1c} reduction in the RHI arm was based on Brunetti et al. [21], while reference rates of hypoglycemia in the RHI arm were based on Home et al. [23] and the split of daytime to nocturnal hypoglycemia was based on Ashwell et al. [31]

CI confidence interval, *HbA_{1c}* glycosylated hemoglobin, *IU* international units, *RR* rate ratio, *SD* standard deviation

[a]Calculations performed with the assumption that 20.2% of non-severe hypoglycemia events were nocturnal

[b]Rate ratio assumed as result was non-significant

from the model by using a rate ratio of 1.0. There was assumed to be no differential effect on other risk factors for rapid-acting analog insulin. Modeled insulin doses in the model were derived from a randomized controlled trial published by Brunetti et al. as insulin doses were not specifically reported in the meta-analyses and the Brunetti et al. trial population was representative of the data reviewed [21].

2.5 Costs and Quality of Life

The analysis was conducted from the perspective of a German healthcare payer and costs were reported in 2015 Euros. The insulin costs in each arm considered the cost of both basal [neutral protamine Hagedorn (NPH) insulin] and bolus insulin, either a rapid-acting insulin lispro injection [rDNA origin] (Humalog®; Eli Lilly and Company, Indianapolis, IN, USA) or regular human insulin. Insulin costs were taken from the 2015 Rote Liste [32]. The total annual cost of insulin per patient was calculated to be €488.72 in the regular human insulin arm and €713.35 in the rapid-acting analog insulin arm. Neutral Protamine Hagedorn was selected as the basal insulin component on the grounds it was the most widely used single insulin in a recent survey of German patients with type 1 diabetes by Laubner et al. with 42.1% of patients using NPH [33]. However, a sensitivity analysis was also conducted in which the per unit cost of the basal component of the insulin regimen was switched to that of insulin glargine (which was used by 38.0% of patients with type 1 diabetes in the Laubner et al. study). In this analysis, total annual per-patient costs of insulin were €604.65 and €849.78 in the human insulin and analog insulin arms, respectively. Costs associated with diabetes-related complications, concomitant medications, and adverse events such as hypoglycemia were taken from published sources for the German setting (Table 3 of the ESM).

Health state utilities were informed by a systematic literature review designed to identify utilities specific to populations with type 1 diabetes (Table 4 of the ESM) [34]. The 'base' utility, assumed to be in patients with diabetes but without complications, was taken to be 0.92 based on 133 patients with diabetes enrolled in a German study that employed the EuroQol-5D instrument to evaluate quality of life [35]. Future costs and clinical benefits were discounted at a rate of 3% per annum in line with the Allgemeine Methoden from the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [36]. Neither the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen nor the Gemeinsamer Bundesausschuss have published a fixed willingness-to-pay threshold below which interventions in different disease areas/indications are deemed to be cost effective as it is considered to run contrary to German Social Security Law [37]. Nevertheless, a reference threshold can be useful as an approximate criterion of cost effectiveness. A hypothetical willingness-to-pay threshold of €30,000 per QALY gained was used in the present analysis based on a number of recently

published cost-effectiveness studies in the German setting [38–40].

2.6 Model Scenarios

The base-case scenario was conducted over a 50-year time horizon based on the rationale that 50 years would be sufficient to capture the onset of late-stage complications. The analysis used the DCCT covariance matrices to covary baseline cohort characteristics and risk factor progressions. Risk factors were set to evolve over time in line with the PRIME Diabetes Model default progressions (rather than remain stable). In 85.2% of patients, HbA_{1c} trended toward a reference target of 7.0% over a 15-year period. The 85.2% of patients was reflective of the patients within 20% of the 6.05% HbA_{1c} target in the DCCT at the end of the study, calculated based on patient-level data from the DCCT. In patients trending towards target, individual patient-level targets were adjusted for patients aged over 40 years (+0.1% per additional 10 years) and for each severe hypoglycemic events experienced in the past 2 years (+0.1% for each event). In the 14.8% of patients not moving towards the target, a sampled 'drift' with a mean value of ± 0.05% was applied in each year in which the patient was more than 20% away from the target. A one-way sensivity analysis was conducted in which all patients were assumed to move towards the treatment target (as opposed to 85.2% based on the DCCT data).

A probabilistic sensitivity analysis was undertaken, in which normal distributions around risk equation parameters were sampled for each patient in each model cycle and non-parametric bootstrapping was performed. For the probabilistic sensitivity analysis, the overall results are presented as well as median (95% credible interval) results from 1000 bootstraps of 2000 patients (i.e., 2000 patients were randomly drawn from the 100,000 patient group 1000 times). Cost and quality-of-life disutility values were assigned an assumed standard deviation of 20% of the mean values and modeled using lognormal distributions.

Cost-effectiveness estimates were also generated for two scenarios in which the modeled characteristics of rapid-acting analog insulin were adjusted. The HbA_{1c} benefit associated with rapid-acting analog insulin was abolished but the change in hypoglycemia rates remained, and the hypoglycemia benefits associated with analog insulin were abolished but the reduction in HbA_{1c} remained. Two further scenarios were then run, one in which the unit cost of basal insulin was switched to that of insulin glargine (in place of the NPH insulin in the base case; dosing assumptions were not changed on the grounds that the modeled patient cohort body mass index was derived from the same study as the dosing assumptions) and a second scenario in which the base-case multiplicative approach to quality-of-life utility coalescing was combined with a diminishing utility model for utilities associated with non-severe hypoglycemia as published by Lauridsen and colleagues in 2014 [41]. With the diminishing utility model, the higher the modeled rates of hypoglycemia, the lower the incremental utility. For instance, based on the Lauridsen et al. study, an annual nocturnal hypoglycemia event rate of 8.55 (as in the rapid-acting analog insulin arm) would yield an average total annual disutility of 0.045 (0.00522 per event), whereas a rate of 16.77 (as in the regular human insulin arm) would yield an average total disutility of 0.056 (0.00332 per event).

3 Results

The clinical trial literature search identified 625 studies, while the meta-analysis search identified 43 studies, of which a total of 33 were duplicates between databases (32 studies and one study in the clinical trial and meta-analysis searches, respectively). Title and abstract screening resulted in the exclusion of 567 studies from the clinical trial search and 36 from the meta-analysis search, leaving 26 clinical trials and six meta-analyses for full-text screening (Figs. 1 and 2 of the ESM). Trials and meta-analyses identified in the literature search indicated that, for adults with type 1 diabetes, rapid-acting analog insulin was associated with benefits in terms of glycemic control (HbA_{1c}) and hypoglycemia risk compared with regular human insulin [23, 24, 31]. The modeled HbA_{1c} progression was in line with the HbA_{1c} model parameters, with patients moving towards the baseline target of 7.0% over 15 years, and the target then gradually increasing with severe hypoglycemic events and increasing patient age (Fig. 3 of the ESM).

Using these data to inform long-term projections with the PRIME Diabetes Model showed that rapid-acting analog insulin therapy was associated with improvements in both survival and quality-adjusted life expectancy compared with regular human insulin (Table 3). In the base-case analysis, discounted life expectancy was projected to be 24.57 years (44.27 years undiscounted) with rapid-acting analog insulin vs. 24.53 years (44.12 years undiscounted) with regular human insulin corresponding to a difference of 0.05 years. Factoring in patient quality of life, rapid-acting analog insulin was associated with a mean discounted quality-adjusted life expectancy benefit of 1.01 quality-adjusted life-years (QALYs) over regular human insulin (12.54 vs. 11.53 QALYs). The reduction in nocturnal hypoglycemia was the biggest driver of improved quality-adjusted life expectancy with rapid-acting analog insulin.

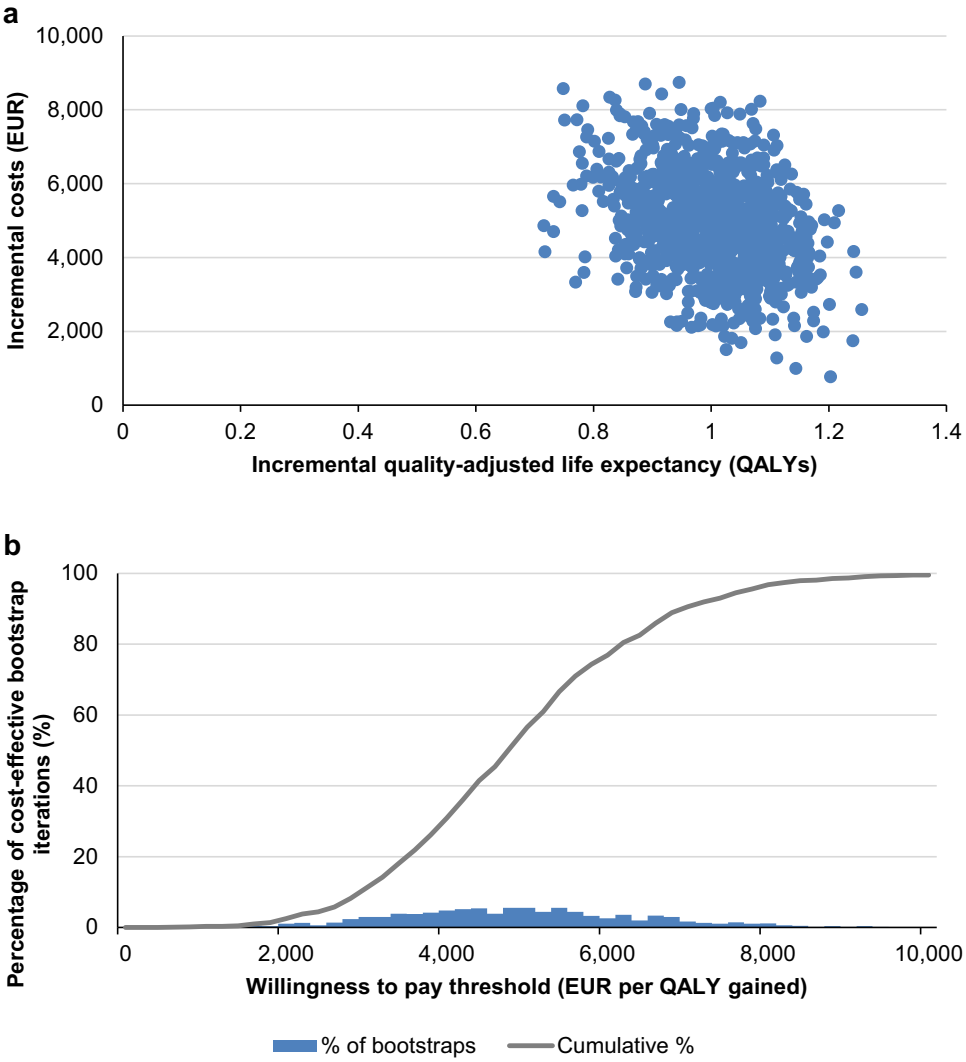

Fig. 1 Cost-effectiveness scatterplot and acceptability curve of rapid-acting analog insulin vs. regular human insulin. The cost-effectiveness plane depicted in **a** indicates the consistent increase in quality-adjusted life expectancy and costs associated with rapid-acting analog insulin relative to human insulin. Incremental cost-effectiveness ratios in all 1000 bootstrap iterations fell below €30,000 (2015 costs) per quality-adjusted life-year (QALY) gained for rapid-acting analog insulin vs. regular human insulin. *EUR*, 2015 Euros

Clinical benefits were accompanied by an increase in mean discounted total direct costs of €4490 per patient for rapid-acting analog insulin (€55,830 vs. €51,340) (Table 3). In combination with modeled effectiveness outcomes, these costs yielded an ICER of €4490 per QALY gained for rapid-acting analog insulin vs. regular human insulin in the base case. Probabilistic sensitivity analyses (a) demonstrated that incremental costs and quality-adjusted life expectancy were relatively insensitive to changes in model assumptions, risk estimates, and risk factors. Over 1000 bootstrapped cohorts, the median ICER was estimated to be €4974 per QALY gained. The ICER was below a willingness-to-pay threshold of €30,000 per QALY gained in all bootstrapped cohorts (b).

A scenario analysis indicated that the reduced hypoglycemia rates associated with rapid-acting analog insulin were the main driver of improved quality-adjusted life expectancy and cost-effectiveness vs. regular human insulin, whereas the small but significant reduction in HbA_{1c} led to an improvement in life expectancy (Table 3). When no HbA_{1c} benefit was associated with rapid-acting analog insulin, the ICER for rapid-acting analog insulin vs. human insulin was 5339 per QALY gained, remaining below a hypothetical willingness-to-pay threshold of €30,000 in the German setting. However, the scenario in which rapid-acting analog insulin was assumed to have no hypoglycemia benefit yielded an ICER of €74,622 per QALY gained, which would be unlikely to be considered cost effective vs. regular human insulin.

The analysis in which the diminishing hypoglycemia utility model was used had a substantial effect on the modeled estimates of quality-adjusted life expectancy, increasing the projections to 16.71 QALYs in the rapid-acting analog arm and 16.46 QALYs in the regular human insulin arm, relative to 12.54 and 11.53 QALYs in the base case, respectively. In this analysis, the ICER increased to €17,765 per QALY gained. The analysis in which the unit cost of insulin glargine was used in place of the cost of

Table 3 Discounted cost and effectiveness outcomes for rapid-acting analog insulin (RAAI) compared with regular human insulin (RHI)

Scenario	Insulin	QALE (QALYs)	Incremental QALE (QALYs)	Cost (€) [2015]	Incremental cost (€)	ICER, € per QALY gained
Base case	RHI	11.53	–	51.340	–	–
	RAAI	12.54	1.01	55.830	4490	4427
No RAAI HbA_{1c} benefit	RHI	11.53	–	51.340	–	–
	RAAI	12.44	0.92	56.227	4887	5339
No RAAI hypoglycemia benefit	RHI	11.53	–	51.340	–	–
	RAAI	11.60	0.07	56.738	5399	74,622
Diminishing hypoglycemia utility model	RHI	16.46	–	51.340	–	–
	RAAI	16.71	0.25	55.830	4490	17,765
Insulin glargine as basal insulin	RHI	11.53	–	54.174	–	–
	RAAI	12.54	1.01	59.172	4998	4928
All patients trending towards HbA_{1c} target	RHI	11.58	–	50.771	–	–
	RAAI	12.58	1.00	55.319	4548	4529

HbA_{1c} glycosylated hemoglobin, *ICER* incremental cost-effectiveness ratio, *QALE* quality-adjusted life expectancy, *QALY* quality-adjusted life-years

NPH insulin for the basal component of the regimen had a negligible effect on outcomes, increasing the incremental cost to €4998 (from €4490 in the base case) and the ICER to €4928 per QALY gained (from €4427 per QALY gained in the base case). Finally, switching the HbA_{1c} progression model to assume that 100% of patients would move towards the HbA_{1c} target resulted in a fractional increase in the ICER to €4529 per QALY gained, driven by a small reduction in incremental quality-adjusted life expectancy and a small increase in incremental cost.

4 Discussion

The outcomes of this long-term modeling analysis, based on a literature review and innovative new diabetes model, indicated that rapid-acting analog insulin regimens were likely to be considered cost effective vs. regular human insulin over the lifetime of patients with type 1 diabetes in Germany. Rapid-acting analog insulin treatment was associated with improvements in life expectancy, quality-adjusted life expectancy, and an ICER of €4427 per QALY gained vs. regular human insulin. These outcomes were based on published clinical data showing that analog insulin was associated with a statistically significant HbA_{1c} benefit and reduced rates of nocturnal and severe hypoglycemia relative to regular human insulin. A scenario analysis showed that quality-adjusted life expectancy benefits projected by the model were driven by reduced hypoglycemia risk with rapid-acting analog insulin therapy. The role of hypoglycemia and its associated disutilities in driving cost-effectiveness analyses in diabetes has been much debated, particularly in the Canadian setting [42]. In the present analyses, abolishing the hypoglycemia benefit associated with rapid-acting analog insulin increased the ICER substantially above a hypothetical willingness-to-pay threshold of €30,000 per QALY in Germany. With the exception of the EURODIAB Study, no German patients were enrolled in the key studies on which the PRIME Diabetes Model is based. However, the combination of model averaging and multi-modeling techniques, and the use of German life tables, cohort characteristics, and cost estimates resulted in an analysis that was well tailored to the German setting.

The analysis in which a published diminishing hypoglycemia utility model was employed to capture non-severe, hypoglycemia-associated quality-of-life decrements yielded an ICER that fell between the base case and the scenario in which hypoglycemia differences were abolished completely. Diminishing utility models yield much more plausible quality-adjusted life expectancy outcomes for events occurring as frequently as non-severe hypoglycemia where the repeated application of even relatively small utility values (0.008 in the present study) can result in inflated differences in modeled quality of life.

A limitation of the study (common to many health economic analyses) was the reliance on relatively short-term data from clinical trials and meta-analyses to make long-term projections. Making long-term projections from short-term data remains one of the essential tenets of health economic modeling and is among the best available options to inform decision making in the absence of long-term clinical trial data. As the projection of outcomes over patient lifetimes is recommended by economic evaluation

guidelines for interventions in chronic conditions such as diabetes, simulation modeling becomes a necessity [43]. Whilst there is always an element of uncertainty around the accuracy of modeling approaches, every effort was made in the present analysis to minimize this, primarily by using a published and validated model of diabetes. Given the use of a validated diabetes model, one of the principal remaining limitations of the present analysis was the quality of the studies included in the Singh et al. meta-analysis from which the HbA_{1c} and hypoglycemia treatment effects were derived. The authors of the meta-analysis noted that the methodological quality of most of the included trials was rated as poor, with the low quality ascribed primarily to the lack of double blinding and poor or absent descriptions of allocation concealment [24]. Despite the methodological concerns, heterogeneity across the trials was low ($I^2 = 0$) for both the HbA_{1c} and severe hypoglycemia endpoints (based on 22 trials including 6021 patients and ten trials including 4502 patients, respectively) and both outcomes were significant at $p < 0.05$.

One notable aspect of the present analysis was the projected increase in life expectancy with rapid-acting analog vs. regular human insulin, which has not been demonstrated in randomized controlled trials in patients with type 1 diabetes. The Singh et al. meta-analysis, on which the HbA_{1c} and hypoglycemia differences were based, reported that there were insufficient data to compare the incidence of diabetes-related complications or death with insulin analogs with conventional insulin [24]. This is potentially owing to the short duration of randomized controlled trials relative to the typical time at risk that elapses before onset of the more severe (and potentially fatal) complications of type 1 diabetes, and is why model-based extrapolation must be employed to project longer term outcomes. The PRIME Diabetes Model uses an interacting system of 42 risk equations and seven risk factor progression equations, all of which have some effect on life expectancy estimates. While the equations are based on numerous sources of data on type 1 diabetes, the projected improvement in life expectancy with rapid-acting analog insulin could be considered analogous to the significant reduction in mortality observed with intensive therapy relative to conventional therapy in the DCCT [44].

The PRIME Diabetes Model has several features that differentiate it from other models of type 1 diabetes, particularly the model averaging approaches to better estimate the risk of cardiovascular complications using data from patients with type 1 diabetes enrolled in the DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) trial, the Swedish National Diabetes Register, EURODIAB, and FinnDiane. The model also incorporates patient-level data to model the progression of risk factors (such as HbA_{1c}) over time and to model realistic relationships between different patient characteristics and treatment effects using a covariance matrix. Covarying patient characteristics in the present analysis resulted in mortality rates that were lower early in the simulation, but subsequently higher than the mortality rates modeled in simulations run without using a covariance matrix. These changes may be owing to different distributions of 'high' and 'low' risk patient characteristics. Without covariance, random assignment of characteristics results in simulated patients with mixtures of both high- and low-risk characteristics, such as high systolic blood pressure and normal body mass index. It is likely that the use of covariance resulted in a simulated cohort of more clinically plausible patients, but further investigation is required to quantify its effects on risk estimates and cost-effectiveness outcomes.

5 Conclusions

Given the growing burden of type 1 diabetes and long-standing concerns around costs associated with the use of analog insulin in its treatment, up-to-date health economic evaluations will become a very important tool for decision makers seeking to optimize therapy and make best use of limited healthcare resources. The reliability of cost-effectiveness and budget impact models to make plausible projections of outcomes becomes fundamentally important in this process. As well as using up-to-date costs, the model must be validated against published clinical data and use the best available data to predict long-term outcomes. In this context, the PRIME Diabetes Model may have advantages over currently available health economic models of type 1 diabetes, being based on recently published data and with all complication risk estimates derived from type 1 diabetes-specific populations. Furthermore, it is one of the first widely available, patient-level simulation models that allows for full exploration of parameter uncertainty and the implementation of risk factor progression and covariance of patient characteristics in type 1 diabetes. The present study showed that, based on published clinical evidence and a new model of type 1 diabetes, rapid-acting analog insulin therapy is likely to be cost effective relative to regular human insulin as the prandial component of basal-bolus insulin regimen in patients with type 1 diabetes in Germany.

Author contributions KSB and KVB devised the research question. All authors were involved in devising the literature search strategy. WJV and RFP then ran the literature searches, screened the retrieved literature, and extracted the data used in the final analyses. All authors were subsequently involved in scrutinizing and, where necessary, revising the simulation plans for the final analyses. RFP ran the

analyses in the PRIME Diabetes Model, which were cross-checked with the original data sources by WJV. RFP and WJV wrote the first draft of the manuscript, with KSB and KVB making substantive revisions prior to submission.

Compliance with Ethical Standards

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Conflict of interest Richard F. Pollock and William J. Valentine are full-time employees of Ossian Health Economics and Communications GmbH, which received consultancy fees from Eli Lilly and Company to conduct the analysis and for the preparation of the manuscript. Kristina S. Boye and Kate Van Brunt are full-time employees of Eli Lilly and Company, which manufactures the rapid-acting insulin Humalog (Insulin lispro) and other antidiabetic agents.

Ethical approval No patient-level data were used as part of the present study. As such, ethics approval and patient consent were neither required nor sought.

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