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ORIGINAL RESEARCH

DEVOTE 5: Evaluating the Short-Term Cost-Utility of Insulin Degludec Versus Insulin Glargine U100 in Basal–Bolus Regimens for Type 2 Diabetes in the UK

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ABSTRACT

Introduction: The aim of this study was to evaluate the short-term cost-utility of insulin degludec (degludec) versus insulin glargine 100 units/mL (glargine U100) for the treatment of type 2 diabetes in the basal–bolus subgroup of the head-to-head cardiovascular (CV) outcome trial, DEVOTE.

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Methods: A cost-utility analysis was conducted over a 2-year time horizon using a decision analytic model to compare costs in patients receiving once daily degludec or glargine U100, both as part of a basal–bolus regimen, in addition to standard care. Clinical outcomes and patient characteristics were taken exclusively from DEVOTE, whilst health-related quality of life utilities and UK-specific costs (expressed in 2016 GBP) were obtained from the literature. The analysis was conducted from the perspective of the National Health Service.

Results: Degludec was associated with mean cost savings of GBP 28.78 per patient relative to glargine U100 in patients with type 2 diabetes at high CV risk. Cost savings were driven by the reduction in risk of diabetes-related complications with degludec, which offset the higher treatment costs relative to glargine U100. Degludec was associated with a mean improvement of 0.0064 quality-adjusted life-years (QALYs) compared with glargine U100, with improvements driven predominantly by lower rates of severe hypoglycemia with degludec versus glargine U100. Improvements in quality-adjusted life expectancy combined with cost neutrality resulted in degludec being dominant over glargine U100. Sensitivity analyses demonstrated that the incremental cost-utility ratio was stable to variations in the majority of model inputs.

Conclusion: The present short-term modeling analysis found that for the basal–bolus

subgroup of patients in DEVOTE, with a high risk of CV events, degludec was cost neutral (no additional costs) compared with glargine U100 over a 2-year time horizon in the UK setting. Furthermore, there were QALY gains with degludec, particularly due to the reduction in the risk of severe hypoglycemia.

INTRODUCTION

Healthcare systems in many countries are under increasing financial pressure due to the demographic challenge of aging populations and the growing burden of chronic diseases, including diabetes [1]. Globally, one in 11 adults (425 million) has diabetes, of which type 2 diabetes makes up around 90% of cases, with the total cost of diabetes to healthcare systems estimated to be USD 727 billion in 2017 [2]. The cost of treating diabetes-related complications is substantial and in many healthcare systems exceeds the cost of blood-glucose-lowering medication [3]. With increasing constraints on healthcare budgets, health economic evaluations, including cost-utility analyses (CUA), are playing an increasingly important role in decisions to allocate resources between therapy areas and interventions. CUA, a special type of cost-effectiveness analysis, compares the costs of new interventions with their outcomes measured in utility-based units, most commonly the quality-adjusted life-year (QALY). This enables the comparison of alternative interventions according to cost per QALY gained, and assists in the efficient allocation of resources to achieve maximum healthcare gains within the constraints of a limited budget [4].

Episodes of severe hypoglycemia are becoming increasingly common, particularly as attention focuses on intensive glycemic control [5–7]. In the Hypoglycaemia Assessment Tool (HAT) study, 8.9% of patients with type 2 diabetes reported an episode of severe hypoglycemia during the 4-week prospective study [8]. Severe hypoglycemic events requiring hospitalization can pose a significant financial burden on healthcare systems: in the UK, the average direct medical cost of an event was estimated at over GBP 1300 in patients with type 2 diabetes [7]. Hypoglycemia has an acute, negative impact on clinical outcomes, including an increased risk of falls, fractures, cardiovascular (CV) events, coma, dementia, neurological conditions, and death, but can also have an adverse effect on longer-term diabetes management due to the fear of hypoglycemia [9–14].

Insulin degludec (degludec) is a basal insulin with an ultralong duration of action and a stable glucose-lowering profile [15]. Studies of the pharmacodynamics of degludec and another long-acting insulin analog, insulin glargine 100 units/mL (glargine U100), have confirmed the lower day-to-day and within-day variability in glucose-lowering effect with degludec compared with glargine U100 [16, 17]. Phase 3 clinical studies have established that similar improvements in glycemic control can be achieved with fewer hypoglycemic episodes, particularly nocturnal hypoglycemia, with degludec versus glargine U100 across a broad spectrum of patients with diabetes [18–20]. Recently, results from the first double-blind, active-comparator cardiovascular outcome trial (CVOT) of a specific antihyperglycemic therapy were published [21, 22]. DEVOTE (NCT01959529) evaluated the CV safety of degludec relative to glargine U100 in patients with type 2 diabetes at a heightened risk of CV complications [22]. In DEVOTE, degludec was noninferior to glargine U100 in terms of the incidence of CV events [22]. Furthermore, the trial demonstrated a significant reduction in the risk of severe hypoglycemia for degludec versus glargine U100 at a similar level of glycemic control [22].

The present evaluation focused on the subgroup of patients who started DEVOTE on a basal–bolus regimen. Guidelines recommend that patients with advanced or very poorly controlled diabetes are managed by basal–bolus therapy [23]. Basal–bolus regimens most closely

mimic the natural pattern of insulin secretion found in individuals without diabetes but are complex and costly, as they require multiple injections per day and therefore an elevated use of consumables such as needles and self-monitored blood glucose (SMBG) tests. This subgroup of patients have advanced type 2 diabetes, and are thus at an increased risk of complications relative to patients with a shorter duration of disease [24]. Zoungas et al. report that for every 5-year increase in diabetes duration, the risk of major adverse cardiovascular events (MACE) and all-cause death increased by 49 and 78%, respectively, when accounting for age at diagnosis [24]. Patients on basal–bolus regimens also have an increased incidence of hypoglycemia relative to those using basal insulin only [25, 26], which can negatively impact quality of life whilst imposing a significant economic burden through increased healthcare resource utilization and loss of productivity [27–29]. The aim of this analysis was therefore to report the clinical outcomes for the basal–bolus subgroup of DEVOTE, and to evaluate the cost-utility of degludec versus glargine U100 in patients treated with a basal–bolus regimen at baseline, over the 2-year trial duration using a simple and transparent decision analytic model in the UK setting.

METHODS

The DEVOTE Trial

DEVOTE was a multinational, treat-to-target, randomized, double-blind, active comparator-controlled CVOT conducted in 20 countries [22]. A total of 7637 patients with type 2 diabetes and at high risk of CV events were randomly assigned to receive either degludec (100 units/mL) or glargine U100, both once daily in addition to standard care [22]. The event-driven trial was designed to continue until the occurrence of at least 633 first MACE—a combined endpoint of non-fatal myocardial infarction (MI), non-fatal stroke, and CV death [22]. Severe hypoglycemia was self-recorded, defined according to the American Diabetes Association as an episode requiring the assistance of another

person to actively administer carbohydrate or glucagon or to take other corrective actions [30]. All outcomes, including severe hypoglycemia, were confirmed by central, blinded review by an independent event adjudication committee. Data on nonsevere hypoglycemia were not collected in DEVOTE.

Basal–Bolus Subgroup Analysis

This analysis used data on clinical outcomes derived from the basal–bolus subgroup of DEVOTE (Table 1, [22]). The basal–bolus subgroup was defined as using basal–bolus (or premix or bolus insulin only) at baseline (before switching to degludec or glargine U100) and constituted 46% ($n = 3515$; degludec, 1760; glargine U100, 1755) of the patients in DEVOTE. Patients on premix regimens were switched to appropriate bolus injections at the start of the trial. Time to first composite MACE, which was the primary outcome measure in DEVOTE and defined as the first occurrence of nonfatal MI, nonfatal stroke, or CV mortality, was analyzed using a Cox proportional hazards regression model on the composite endpoint. The number of severe hypoglycemic episodes was analyzed using a negative binomial regression model with a log-link function and log(duration of observation time) as offset. Death from other causes, i.e., death from causes other than first MACE, was analyzed using a Cox proportional hazards regression model. Insulin dose (units/kg) was log-transformed and analyzed with a mixed model for repeated measures (MMRM) within subjects using an unstructured residual covariance matrix among visits. Visit interactions with age, dose at baseline, body mass index, alternative titration target (yes/no), and treatment were included in the model as fixed effect covariates. Change from baseline in HbA_{1c} to the 24-month visit was analyzed using an MMRM within subjects using an unstructured residual covariance matrix among visits at 6, 12, and 24 months of the trial; interactions between visit and treatment and between visit and baseline HbA_{1c} were included as fixed effects in the model.

Table 1 Clinical outcomes from the DEVOTE basal–bolus subgroup

	Degludec/glargine U100 ratio	SE	95% CI	P value[a]	Annual event rate per PYE	
					Glargine U100	Degludec[b]
Complications						
First MACE	0.81[c]	0.10	[0.66; 0.98][c]	0.035	0.0607	0.0489
Severe hypoglycemia	0.63[c]	0.15	[0.47; 0.85][c]	0.002	0.0850[c]	0.0536[c]
Death from other causes	0.77	0.19	[0.53; 1.12]	0.165	0.0179	0.0179
	ETR (degludec/glargine U100)	SE	95% CI	P value	Mean dose (units)	
					Glargine U100	Degludec[b]
Insulin dose						
Basal insulin						
Baseline	N/A				49.0	49.0
12 months	1.03	0.02	[1.00; 1.06]	0.050	65.1	65.1
24 months	1.06	0.02	[1.02; 1.10]	0.007	70.4	74.7
Bolus insulin						
Baseline	N/A				39.4	39.4
12 months	0.95	0.02	[0.91; 1.00]	0.050	59.5	59.5
24 months	0.96	0.04	[0.89; 1.03]	0.204	69.7	69.7

CI confidence interval, *ETR* estimated treatment ratio, *glargine U100* insulin glargine 100 units/mL, *MACE* major adverse cardiovascular event, *N/A* not applicable, *PYE* patient-years of exposure, *SE* standard error

[a] *P* value refers to two-sided test of degludec/glargine U100 ratio = 1.0

[b] Estimated by applying degludec/glargine U100 ratio if statistically significant, otherwise glargine U100 value

[c] Previously reported in the DEVOTE primary manuscript supplementary appendix [22]

Model Overview

A decision analytic model (Fig. 1, [30]) was developed to evaluate the cost-utility of degludec versus glargine U100 using clinical data from the basal–bolus subgroup of patients with type 2 diabetes from DEVOTE. The analysis was conducted for the UK setting from the perspective of the National Health Service (NHS). Baseline characteristics for the simulated patient cohort were based on the DEVOTE basal–bolus subgroup (Table S1 in the Electronic supplementary material, ESM). The model was a short-term cohort model with two annual cycles capturing first MACE, death from other causes, severe hypoglycemic events, and insulin dose. HbA$_{1c}$ was not captured in the analysis given the short time horizon and the treat-to-target trial design of DEVOTE, resulting in similar end-of-trial HbA$_{1c}$ levels in both treatment arms [22]. The model used relative rates (hazard, rate, and dose ratios) from regression analyses to estimate differences between the degludec and glargine U100 treatment arms (Table 1). In line with previous evaluations of degludec, the model only included treatment effects for which a statistically significant difference between treatment arms was
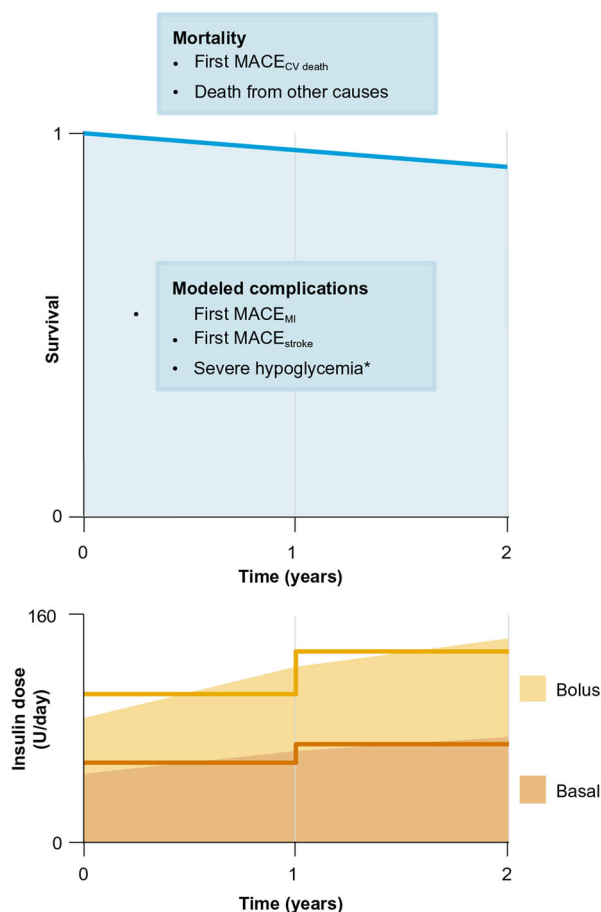
Fig. 1 Schematic of the cost-utility model. Diagram shows the model as run for each treatment arm (degludec and glargine U100). The model used relative rates (hazard, rate, and dose ratios) from regression analyses to derive the rates and doses in the degludec arm (see the 'Model Overview' section). * Severe hypoglycemia was defined according to the American Diabetes Association as an episode requiring the assistance of another person to actively administer carbohydrate or glucagon or to take other corrective actions [30]. *CV* cardiovascular, *glargine U100* insulin glargine 100 units/mL, *MACE* major adverse cardiovascular event, *MI* myocardial infarction, *U* units

documented, and assumed that all other differences were due to random variation (i.e., the null hypothesis could not be rejected). However, nonsignificant differences were explored in the sensitivity analyses. An annual discount rate of 3.5% was applied to the costs and clinical benefits in the second cycle [31]. Model outputs include the average cost in pounds sterling (GBP), utility outcomes in QALYs for each arm,

the inter-arm differences in cost and QALYs, and the incremental cost-utility ratio (ICUR; cost per QALY gained).

Cost Data and Resource Use

Treatment unit costs were based on UK list prices (Table 2, [32–37]). It was assumed that four injections per day were administered for the basal–bolus regimen (same in both arms) and a new needle and SMBG test strip and lancet were used per injection. Mean doses of basal and bolus insulin were estimated for each of the annual cycles and adjusted for survival. Insulin treatment costs were modeled as the unit cost multiplied by the mean annual dose, calculated as the arithmetic mean of the start- and end-of-year doses captured from the clinical trial data to approximate the average under the curve (Table 1b). Costs of complications were derived from the literature and inflation-adjusted to 2016 prices using the hospital and community health services index from the Personal Social Services Research Unit [37] (Table 2). For nonfatal MI and nonfatal stroke, an event cost was captured in the cycle in which the event took place and a state cost was captured in the subsequent year, reflecting ongoing excess healthcare resource use after the event (only relevant for first-year events given the 2-year time-horizon). Costs of severe hypoglycemia were captured exclusively in the year of the event, and were a summary of direct costs for patients who were treated by a family member or friend, or received emergency treatment from a paramedic or general practitioner, or received treatment in a hospital [34]. Cost estimates of severe hypoglycemia included immediate direct treatment costs (attendance by a healthcare professional, ambulance callout, and administration of medications) and follow-up treatment costs (additional visits to see a general practitioner, extra blood glucose test strips, and patient/family education).

Event Rates

Rates from DEVOTE for first MACE, death from other causes, and severe hypoglycemic events

Table 2 Input parameters

Parameter	Value	Unit	Source
Treatment costs			
Glargine U100 unit price[a]	0.0277	GBP	MIMS [32]
Degludec unit price[b]	0.0311	GBP	MIMS [32]
IAsp unit price[c]	0.0204	GBP	MIMS [32]
Needle unit price[d]	0.0969	GBP	MIMS [32]
SMBG test strip unit price[e]	0.3678	GBP	MIMS [32]
Complication costs			
MI, nonfatal	7718.85	GBP	Alva et al. 2015 [33] (inflation-adjusted)[f]
Stroke, nonfatal	8301.28	GBP	Alva et al. 2015 [33] (inflation-adjusted)[f]
CV death	0	GBP	
Year 2 MI	1918.67	GBP	Alva et al. 2015 [33] (inflation-adjusted)[f]
Year 2 stroke	1977.55	GBP	Alva et al. 2015 [33] (inflation-adjusted)[f]
Severe hypoglycemia	414.09	GBP	Hammer et al. 2009 [34] (inflation-adjusted)[f]
Utilities			
Base	0.785	Utility	Clarke et al. 2002 [35]
MI	− 0.055	Disutility	Clarke et al. 2002 [35]
Stroke	− 0.164	Disutility	Clarke et al. 2002 [35]
Severe hypoglycemia	− 0.057	Disutility	Evans et al. 2013 [36]

CV cardiovascular, *GBP* pounds sterling, *IAsp* insulin aspart, *glargine U100* insulin glargine 100 units/mL, *MI* myocardial infarction, *MIMS Monthly Index of Medical Specialities*, *SMBG* self-monitored blood glucose

[a] Lantus® (in Solostar® pen) £41.50 for 1500 units

[b] Degludec (in FlexTouch® pen) £46.60 for 1500 units

[c] Insulin aspart (in FlexPen®) £30.60 for 1500 units

[d] BD MicroFine® 5 mm: £9.69 per 100 needles

[e] SMBG test costs based on the use of one Accu-Chek® Aviva test strip (£15.96 for 50 units) and one Accu-Chek® FastClix lancet (9.92 for 204 units) per test

[f] Inflation-adjusted to 2016 prices using the hospital and community health services index from the Personal Social Services Research Unit [37]

were captured in the model. Adopting a conservative approach, subsequent CV events after first MACE were not incorporated into the CUA. The model used CV death from first MACE as well as death from other causes to estimate annual survival, which was applied in each of the two annual cycles. Annual nonfatal MI, nonfatal stroke, and severe hypoglycemic event

rates were applied to the surviving proportion of the cohort in the two annual cycles (Fig. 1).

Utility Data

Baseline utility and disutility values were identified in the literature (Table 2). For nonfatal MI and nonfatal stroke, the utilities were half-

cycle-corrected in the first year and applied fully in the subsequent year (only relevant for first-year events given the 2-year time horizon). The severe hypoglycemia disutility was an annualized disutility for the year of the event. The model was developed to optionally capture an "extension period," allowing additional costs and quality of life estimates over a longer time horizon to be attached to the events that occurred in the within-trial period, i.e., four scenarios based on a nonfatal MI, nonfatal stroke, no MACE, or death in the trial. Extending the analysis with additional costs was explored in a sensitivity analysis.

Sensitivity Analyses

Deterministic sensitivity analyses (of the effects of individual changes in model parameters on clinical and cost outcomes) were performed based on no discounting, the inclusion of nonsignificant differences between treatment arms, the use of the same MACE distribution for degludec and glargine U100, alternative unit costs and disutilities, the inclusion of a utility for flexible dosing, and the inclusion of long-term additional costs and effects based on scenarios run in the IQVIA CORE Diabetes Model version 9.0 (IQVIA, Basel, Switzerland) [using updated UKPDS 82 CV risk equations], assuming the same rescue medication in both arms (Fig. S1 in the ESM) and extension parameters detailed in Table S2 of the ESM.

A probabilistic sensitivity analysis (PSA) was performed to quantify the effect of statistical uncertainty around the input parameters on the model results. Uncertainty was captured based on standard errors around the DEVOTE outcomes, which were used to inform the shape of a series of normal and lognormal distributions around model parameters (Table S3 of the ESM). PSA outcomes were based on 1000 model iterations, sampling from all modeled distributions in each iteration without capturing covariance.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Basal–Bolus Subgroup Analysis

The risk of experiencing the primary composite outcome of 3-component MACE was 19% lower with degludec versus glargine U100 (hazard ratio, 0.81; 95% CI 0.66–0.98; $P = 0.035$) (Table 1a). This hazard ratio was applied to the annual rate of first MACE observed in the glargine U100 arm of 0.0607 events/patient-year of exposure (PYE) to estimate a rate of 0.0489 events/PYE for the degludec arm. The distribution of components within the composite MACE endpoint for degludec versus glargine U100 (events/PYE) was nonfatal MI (0.0208 [42%] vs. 0.0292 [48%]), nonfatal stroke (0.0099 [20%] vs. 0.0124 [20%]), and CV death (0.0182 [37%] vs. 0.0191 [31%]). There was a 37% lower risk of severe hypoglycemia with degludec versus glargine U100 (estimated rate ratio, 0.63; 95% CI 0.47–0.85; $P = 0.002$) (Table 1a). This ratio was applied to the annual rate of severe hypoglycemia observed in the glargine U100 arm of 0.085 to result in an estimated annual rate of 0.0536 episodes of severe hypoglycemia for degludec. There was no significant difference in the incidence of death from other causes (excluding first MACE) between treatment arms (Table 1a). The only significant difference in insulin dose between treatment arms was for basal insulin dose at 24 months, which was higher in the degludec arm (Table 1b). There was no significant difference in change from baseline in HbA$_{1c}$ after 24 months between treatment arms (Table S4 of the ESM).

Base Case

In our evaluation of discounted costs, the mean cost per patient was GBP 4002.36 in the degludec arm compared with GBP 4031.13 in the glargine U100 arm. This resulted in a negligible cost saving of GBP 28.78 per patient with degludec over the 2-year time horizon. Savings were driven by a reduction in the risk of diabetes-related complications with degludec, particularly nonfatal MI, which more than offset the higher acquisition costs compared with

Table 3 Short-term cost-utility outcomes of treatment with degludec versus glargine U100 (base case analysis)

	Degludec	Glargine U100	Difference (Degludec − glargine U100)
Costs (GBP)			
Total costs	4002.36	4031.13	− 28.78
Treatment costs			
Basal insulin	1361.02	1191.06	169.96
Bolus insulin	802.01	801.21	0.80
Basal needles	67.12	67.06	0.06
Bolus needles	201.37	201.18	0.19
Routine SMBG test	1019.17	1018.22	0.95
Costs of complications			
Nonfatal MI	336.64	470.81	− 134.18
Nonfatal stroke	172.42	214.02	− 41.60
Severe hypoglycemia	42.61	67.58	− 24.96
Effects (QALYs)			
Total QALYs	1.4778	1.4715	0.0064
QALY breakdown			
Baseline	1.4888	1.4874	0.0014
Nonfatal MI	− 0.0021	− 0.0030	0.0009
Nonfatal stroke	− 0.0031	− 0.0038	0.0008
Severe hypoglycemia	− 0.0057	− 0.0091	0.0034
Incremental cost-utility ratio			
ICUR (cost/QALY)			Dominant[a]

Costs and QALYs are discounted by 3.5%

GBP pounds sterling, *glargine U100* insulin glargine 100 units/mL, *ICUR* incremental cost-utility ratio, *MI* myocardial infarction, *QALY* quality-adjusted life-year, *SMBG* self-monitored blood glucose

[a] Dominant, improved quality of life at lower or similar cost

glargine U100 (Table 3). Total discounted QALYs were estimated at 1.4778 and 1.4715 for degludec and glargine U100, respectively, with an increment of 0.0064 in favor of degludec. The main drivers of this were the risk reductions for severe hypoglycemia and (to a smaller extent) nonfatal MI and nonfatal stroke with degludec compared with glargine U100 (Table 3). An ICUR is not shown, per convention, as the result was "dominant," meaning that an improvement in health is observed together with cost savings/cost neutrality.

Sensitivity Analyses

The deterministic sensitivity analyses demonstrated that the base-case findings remained largely unchanged despite variation in a range of model input values, with ICURs showing dominance or close to cost neutrality in most cases. Using the same MACE distribution (the glargine U100 MACE distribution) in both treatment arms changed the results, lowering CV mortality at the expense of the nonfatal MI reduction, which increased the QALYs gained in

the degludec arm but lowered the cost offsets. Changing the treatment costs (a 15% lower glargine U100 cost) resulted in an ICUR in the lower range of £20,000–£30,000 per QALY gained, although when long-term extension costs and effects were included, degludec was still highly cost-effective (Table 4, [38–45]). The probabilistic sensitivity analyses showed that degludec is likely to be cost-effective with 96.5 and 97.7% probabilities for willingness-to-pay thresholds of £20,000 and £30,000 per QALY gained, respectively (Fig. 2).

DISCUSSION

In this analysis of the basal–bolus subgroup of DEVOTE, there was a 19% lower risk of MACE and a 37% lower risk of severe hypoglycemia with degludec versus glargine U100. The results of the CUA showed that for the basal–bolus subgroup of patients in DEVOTE, with a high risk of CV events, degludec was cost neutral (no additional cost) compared with glargine U100 over a 2-year trial horizon in the UK setting. The higher acquisition costs with degludec were more than offset by the lower costs associated with a reduced risk of diabetes-related complications, particularly MI, with degludec versus glargine U100. Furthermore, there were QALY gains with degludec, particularly due to the reduction in risk of severe hypoglycemia.

Limiting the risk of hypoglycemia is important for both patients and physicians [46, 47]. Severe hypoglycemia is associated with an increased frequency of various adverse outcomes in patients with diabetes, including CV disease, MACE, dementia (in older patients), major microvascular events, and death [10–14]. Hypoglycemia can have considerable negative effects on patient quality of life [48], with an increasing frequency and severity of events associated with a reduced quality of life [47]. The long-term effects of hypoglycemia may include behavioral changes and significant anxiety or fear of future episodes [47]. Fear of hypoglycemia can adversely affect diabetes management and clinical outcomes by compromising adherence to medications [9].

Previous health economic evaluations from a NHS perspective have reported similar results, with degludec considered dominant or cost-effective relative to glargine U100 in the UK setting across diabetes types and regimens (basal only or basal–bolus) [49–51]. These results were based mainly upon differences in event rates (and associated costs) of severe and nonsevere hypoglycemia, whilst CV events and death from other causes (excluding first MACE) were not captured by the models [49–51]. With the present analysis using data from a CVOT, CV outcomes and death from other causes were included. However, data on nonsevere hypoglycemia, a large driver of QALYs in other reported evaluations, were not collected and therefore could not be included in our evaluation. Hypoglycemia exerts significant societal costs through lost productivity related to absences from work [52] that were not reflected by our CUA from a NHS perspective.

In the overall trial population of DEVOTE, degludec was noninferior to glargine U100 with respect to the incidence of first MACE (hazard ratio, 0.91; 95% CI 0.78–1.06) [22]. Here, we report that the risk of first MACE was significantly lower with degludec versus glargine U100 in the basal–bolus subgroup of DEVOTE. The more pronounced treatment difference for MACE in the basal–bolus subgroup of DEVOTE compared with the full trial population may be explained by the more advanced disease in these patients and thus a higher risk of diabetes-related complications such as MACE [24]. This is evidenced by the higher proportion of patients that experienced first MACE who started DEVOTE on a basal–bolus regimen (9.8% with degludec vs. 12.0% with glargine) compared with the full trial population (8.5% with degludec vs. 9.3% with glargine U100) [22].

Recently published and currently ongoing CVOTs of antihyperglycemic therapies are usually placebo-controlled, noninferiority trials lacking an active comparator [53]. DEVOTE is the first published double-blind CVOT that compared the drug of interest head-to-head with an active comparator—in this case degludec versus glargine U100, both once daily in addition to standard care [21, 22]. This strategy allows a direct comparison of treatment effects,

Table 4 Results of the deterministic sensitivity analyses

Parameter	Sensitivity analysis		ΔCosts (GBP)	ΔQALY	ICUR (GBP per QALY gained)
Base case			− 28.78	0.0064	Dominant
No discounting	Discount rate = 0%		− 28.85	0.0065	Dominant
Insignificant difference	All RRs and HRs applied regardless of P value		− 19.65	0.0126	Dominant
Same MACE distribution	Glargine U100 MACE distribution applied in the degludec arm		27.71	0.0102	2705
CV costs [38]	MI Y1	5687[a]	5.66	0.0064	891
	MI Y2+	639[a]			
	Stroke Y1	9567[a]			
	Stroke Y2+	2572[a]			
CV disutilities [39]	MI	− 0.047	− 28.78	0.0058	Dominant
	Stroke	− 0.060			
CV disutilities [40]	MI Y1	− 0.129	− 28.78	0.0074	Dominant
	MI Y2+	− 0.078			
	Stroke Y1	− 0.181			
	Stroke Y2+	− 0.269			
CV disutilities [41]	MI	− 0.026	− 28.78	0.0056	Dominant
	Stroke	− 0.099			
Cost of CV death [33]	3238[a,b]		− 34.51	0.0064	Dominant
Flex utility [42][c]	0.006		− 28.78	0.0177	Dominant
Flex utility [43][c]	0.013		− 28.78	0.0310	Dominant
Hypoglycemia cost [44]	93.12[a]		− 9.35	0.0064	Dominant
Hypoglycemia disutility [45]	0.0118[d]		− 28.78	0.0037	Dominant
Glargine U100 price	− 15%		149.88	0.0064	23579
Additional long-term costs and effects	Extension[e]		− 76.45	0.0344	Dominant

Table 4 continued

Parameter	Sensitivity analysis	ΔCosts (GBP)	ΔQALY	ICUR (GBP per QALY gained)
Combination of above two	Extension and glargine U100 − 15% cost[e]	102.21	0.0344	2971

Δ difference in, *CV* cardiovascular, *GBP* pounds sterling, *HR* hazard ratio, *ICUR* incremental cost-utility ratio, *glargine U100* insulin glargine, *MACE* major adverse cardiovascular event, *MI* myocardial infarction, *RR* risk ratio, *QALY* quality-adjusted life-year, *Y1* year one, *Y2+* year two onwards

[a] Inflation-adjusted to 2016 prices using the hospital and community health services index from the Personal Social Services Research Unit [37]

[b] Average cost of fatal MI, fatal stroke, and fatal ischemic heart disease [33]

[c] Flex utility refers to the convenience of flexible dosing times with degludec

[d] Adjusted to 1-year time horizon based upon one severe event in the past 3 months causing a 4.7% loss of utility

[e] See Table S2 of the ESM for long-term modeling extension parameters

and represents an improvement in the design of CVOTs [53]. To the authors' knowledge, this is the first health economic analysis of a specific antihyperglycemic therapy to use data sourced from a double-blind, active-comparator CVOT. This enabled clinical data for the base-case analysis for both treatment arms to be derived from a single homogeneous source (the basal–bolus subgroup of the DEVOTE study population) including observed event rates for MACE, death from other causes, and severe hypoglycemia. Additional strengths of this CUA include the exclusive use of endpoints with significant differences between treatment arms; that the base-case findings remained largely unchanged despite variation in a range of model input values in the sensitivity analyses; and the conservative assumptions of the base-case analysis, which did not include long-term improvements.

This study also has several limitations. Foremost, the evaluation is based on a subgroup of patients, which affects the generalizability of the results beyond patients at high risk of CV events and treated with basal–bolus regimens. Notwithstanding, the internal validity for this group of patients is high. Decision analytic models, such as the one used in the present analysis, bring together evidence from various sources to model cost-utility in a specific setting, in this case the UK cost setting, and are always associated with some uncertainty arising from the model design and input parameters. Many of the factors contributing to the uncertainty have been explored in sensitivity analyses, which supported the results of the base-case model and suggest that the findings are robust. A further limitation is the omission of microvascular complications from the analysis. While microvascular complications can have a sizeable effect on diabetes-related treatment costs and patient quality of life, no microvascular endpoints were included in the DEVOTE trial. The rationale for their exclusion was driven primarily by the desire to maintain the homogeneity of the clinical data [33, 54]. Finally, the time horizon in this analysis was limited by the duration of the trial. It could be perceived as being overly conservative to limit a CV benefit to only two years. However, a longer-term (lifetime) perspective was explored in a sensitivity analysis which assumed rescue medication in both arms and no continued benefits after the trial period beyond differences in the modeled history of events in the two model arms. Further analyses would be required to quantify the potential long-term costs and benefits based on possible scenarios of the protective effects of degludec on CV risk and severe hypoglycemia.

(a)

(b)
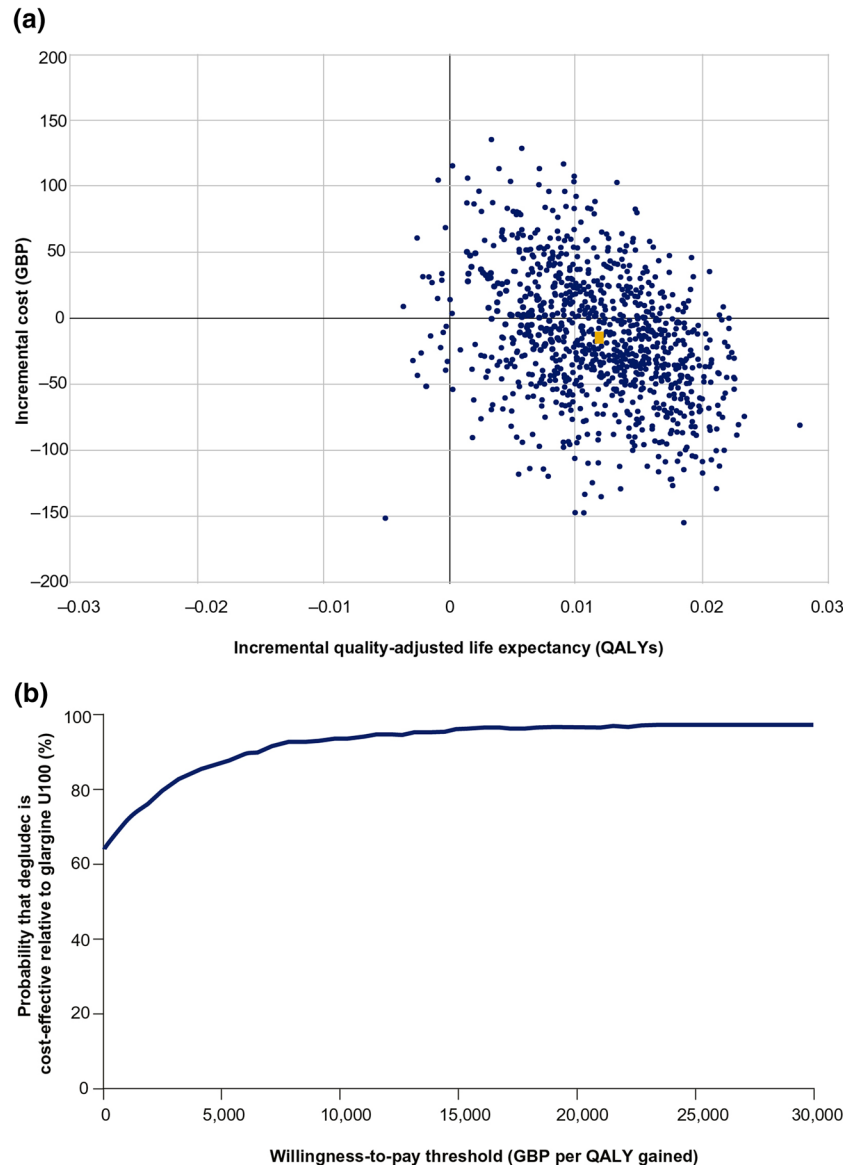
Fig. 2a–b Probabilistic sensitivity analysis results: **a** cost-utility scatterplot; **b** cost-utility acceptability curve. In **a**, the orange square represents the average value for incremental cost and incremental quality-adjusted life expectancy. *GBP* pounds sterling, *glargine U100* insulin glargine 100 units/mL, *QALY* quality-adjusted life-years

CONCLUSION

Based on this short-term modeling analysis, degludec provides improvements in clinical outcomes at no additional cost in the UK setting, as compared with glargine U100 in patients with type 2 diabetes at high risk of CV events who are treated with a basal–bolus insulin regimen.

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