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Original article

Insulin degludec early clinical experience: does the promise from the clinical trials translate into clinical practice—a case-based evaluation

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Abstract

Background:
Clinical experience of patients is an additional source of information that can inform prescribing decisions for new therapies in practice. In diabetes, for example, patients with recurrent hypoglycemia may be excluded from trials conducted for regulatory purposes. Using insulin degludec (IDeg), a new basal insulin with an ultra-long duration of action as an example, an interim analysis is presented describing whether the decision to prescribe IDeg to patients experiencing treatment-limiting problems on their existing insulin regimes represented good clinical and economic value.

Methods:
Records from the first 51 consecutive patients with diabetes (35 type 1 [T1D] and 16 type 2 [T2D]) switching to insulin degludec from either insulin glargine (IGlar) or insulin detemir (IDet), mostly due to problems with hypoglycemia (39/51, 76.5%), were reviewed at up to 37 weeks. Patients indicated frequency of hypoglycemia and completed a disease-specific questionnaire reporting six measures of confidence and treatment satisfaction. For the largest group of exposed patents, the T1D module of the IMS Core Diabetes Model (CDM) was used to evaluate the cost-effectiveness of the treatment decision.

Findings:
HbA_{1c} decreased by $0.5 \pm 0.3\%$ points and $0.7 \pm 0.3\%$ points for T1D and T2D, respectively. Hypoglycemic events decreased by >90%. Combined mean scores were ≥ 3.7 (1 = much worse, 3 = no change, 5 = much improved) for all six satisfaction and confidence items. In T1D, the treatment decision was highly cost-effective in the CDM lifetime analysis. Even when excluding benefits beyond hypoglycemia reduction, predicted cost per quality-adjusted life-year for IDeg vs IGlar/IDet was £10,754.

Interpretation:
These data illustrate the complementary nature of clinical trial and practice data when evaluating the value of therapeutic innovations in diabetes care. There were reductions in patient-reported hypoglycemia, reduced HbA_{1c}, and improved treatment satisfaction in relation to the decision to prescribe IDeg. Initial health economic evaluation suggested that the decision to prescribe IDeg in this phenotypic group of T1D patients represented good value for money.

Introduction

When new technologies are introduced to clinical practice, there may be a gap in the literature, with most data being derived from the highly selected populations of phase 3 clinical trials and with limited reports of outcomes in the more diverse population of patients who are encountered in real-world practice. In diabetes, for example, patients with recurrent hypoglycemia may be excluded from trials conducted for regulatory purposes. Thus, when clinicians are

considering whether to prescribe a new product for their patients, additional data from real-world experience may help inform their clinical decisions. Such data can be obtained from patient registries, from phase 4 trials, from observational cohort studies, and from clinical experience. Insulin degludec is a new basal insulin with a novel mechanism of protraction[1] that produces a flat glucose-lowering profile[2,3] and confers an ultra-long duration of action (>42 h)[4], and less variability in glucose-lowering action from injection to injection than insulin glargine[5]. Using insulin degludec as an example, we present an interim analysis describing how the decision to prescribe insulin degludec to patients experiencing treatment-limiting problems on their previous basal insulin was supported by initial clinical and economic outcomes at a single centre in the UK.

Clinical background

One of the most important clinical concerns with any glucose-lowering treatment in diabetes is hypoglycemia. Hypoglycemia is a concern in both type 1 (T1D) and type 2 (T2D) diabetes and is associated with a lower health-related quality-of-life, an increased burden of depression, a variety of undesirable compensatory behaviors by patients, and continues to be a major treatment-limiting factor in achieving optimal glycemic control[6–15]. Furthermore, emergency treatment for hypoglycemia is associated with significant economic costs[16]. Given this spectrum of adverse consequences, recent guidelines continue to emphasize the importance of individualizing therapy and prioritizing treatment regimens that minimize risk of hypoglycemia for each patient[14,17,18].

Numerous randomized, controlled, phase 3a treat-to-target trials in T1D and T2D[19–25] provide evidence that the novel pharmacokinetic and pharmacodynamic properties of insulin degludec may translate into a lower risk of hypoglycemia, and nocturnal hypoglycemia in particular, including people with T1D[19,21,22], people with T2D who were insulin naïve[23,24], and people with T2D who were prevalent insulin users[26]. Due to the regulatory nature of these studies, patients at high risk of hypoglycemia or experiencing recurrent hypoglycemia were excluded, in order to maximize the quality of data capture.

Despite this consideration, the potential hypoglycemic advantages of insulin degludec were summarized across trials via a pre-specified meta-analysis of pooled patient-level data (2899 people randomized to insulin degludec and 1431 randomized to insulin glargine) from seven of these trials (two trials in T1D and five trials in T2D)[27]. In that meta-analysis, significantly lower rates of hypoglycemia were reported for insulin degludec vs insulin glargine in the overall T2D population (rate ratio [95% CI] = 0.83 [0.74; 0.94] and 0.68 [0.57; 0.82], for overall confirmed and nocturnal confirmed hypoglycemia, respectively), during the entire treatment period. In the same metanalysis, for T1D, the rates were not significantly different for insulin degludec vs insulin glargine during the entire treatment period (rate ratio = 1.10 [0.96; 1.26] or during the maintenance period (rate ratio = 1.02 [0.88; 1.19]), but were significantly lower for insulin degludec vs insulin glargine for confirmed nocturnal hypoglycemia during the maintenance period (rate ratio = 0.75 [0.60; 0.94]).

As a further measure of its potential clinical utility, data from these phase 3 trials indicate that insulin degludec is associated with improved measures of treatment satisfaction[28] and improved health-related quality-of-life (health utility)[29], compared with insulin glargine. Finally, treatment regimens with improved convenience (i.e., a flexible daily-dosing scheme for insulin degludec[23] or a more concentrated (200 U/mL) formulation of insulin degludec allowing a smaller injection volume) were also evaluated in trials in patients with T2D[20], with no detrimental impact on either glucose control or the risk of hypoglycemia.

The generalizability of these observations to a wider patient population remains unclear, while the results of studies with insulin degludec in more hypoglycemia prone patients are awaited.

Health economic outcomes should also be considered when evaluating a new insulin analog. For example, previous health economic evaluations from real-world patient samples in the UK comparing the first wave of insulin analogs with neutral protamine Hagedorn (NPH) have demonstrated how factors such as baseline demographics, changes in treatment and physiological parameters can be taken into account to project total direct costs (treatment plus complications) of an intervention over a patient's lifetime[30,31]. Recently, a cost-utility analysis was performed comparing insulin degludec vs insulin glargine in people with T1D or insulin-treated T2D[32]. Rate ratios for hypoglycemia for insulin degludec were derived from the meta-analysis discussed above[27], and those for insulin glargine were derived from 603 patients with diabetes in Sweden who were participating in a larger European observational study[33]. Results indicated that insulin degludec was associated with gains in quality-adjusted life years (QALY) compared with insulin glargine in all three populations, mostly due to reduced hypoglycemia[32]. Short-term modeling using a meta-analysis of data from phase 3 clinical trials has shown that insulin degludec is a cost-effective treatment option vs insulin glargine, and was highly cost-effective for patients experiencing ≥1 hypoglycemic event per year (incremental cost-effectiveness ratio of £2625–£4887 per QALY[34].

Given this background, insulin degludec was prescribed for a series of consecutive patients who were experiencing treatment-limiting problems with hypoglycemia on

alternative basal insulin regimens (insulin detemir or insulin glargine). Here we report interim results from that case series, as well as a preliminary evaluation of the cost-effectiveness profile of insulin degludec in the sub-group of patients with T1D, in an attempt to illustrate how data derived from clinical practice experience may be employed to inform on the economic and clinical value of new technologies beyond the data available from regulatory trials.

Methods

In this retrospective, single-center case series analysis, records from the first consecutive 51 patients (35 T1D and 16 T2D; 24 male, 27 female) who had switched to insulin degludec from either insulin glargine or insulin detemir were assessed. Patients were switched from their previous insulin on a unit-for-unit basis if administering once daily. For those switching to insulin degludec from a twice-daily regimen, the dose was reduced by 10%, irrespective of type of diabetes. The choice of formulation of insulin degludec (100 U/mL or 200 U/mL) was contingent on the concentration needed to deliver the required daily dose in a single injection. The two formulations have been shown to be bioequivalent and to have similar pharmacodynamic profiles at steady state, and, therefore, can be used interchangeably[3].

Patient demographic data, diabetes history, and baseline glucose control data were obtained from medical records. Hypoglycemia was defined as patient-reported events or self-measured blood glucose <4 mmol/L. Patients were followed for up to 37 weeks (mean [SD] = 25.5 ± 6.0 weeks). At most recent visit, patients indicated frequency of hypoglycemia during the preceding 4 weeks. Each patient also completed a brief, disease-specific generic questionnaire indicating any changes in confidence in the effectiveness of their diabetes treatment and making insulin dose adjustments, fear of hypoglycemia, predictability of blood–glucose measures, concern about living with diabetes, and overall satisfaction with treatment following initiation of insulin degludec. These data were evaluated descriptively and percentage changes in clinical variables from baseline to most recent visit were calculated.

Health economic evaluation

The IMS CORE Diabetes Model (CDM) is an established Internet-based tool that allows estimation of cost-effectiveness of interventions in diabetes[35]. Figure 1 represents an overview of the CDM. The CDM facilitates comparison of different diabetes management strategies in various patient populations in realistic clinical settings and has been validated against 66 epidemiological and clinical studies ($R^2 = 0.9224$)[36]. The range of important complications of diabetes are accounted for in the CDM by a series of Markov models using Monte Carlo simulation to include state, time in state, and probabilities. The most current published sources are used for deriving these probabilities.

For this analysis, the T1D module of CDM was used to evaluate the cost effectiveness of insulin degludec compared to insulin glargine or insulin detemir in people with T1D experiencing hypoglycemia using one of these other basal insulins (insulin glargine/insulin detemir group). Efficacy data were derived from individual patient source data drawn from the chart review of people with T1D converted from insulin glargine/insulin detemir to insulin degludec. CDM cohort profiles were generated reflecting patient profiles associated with insulin glargine/insulin detemir prior to initiating insulin degludec (the comparison arm) and following initiation of insulin degludec (the intervention arm). The model was run over a lifetime and the benefits and UK derived costs were discounted at 3.5%.

Results

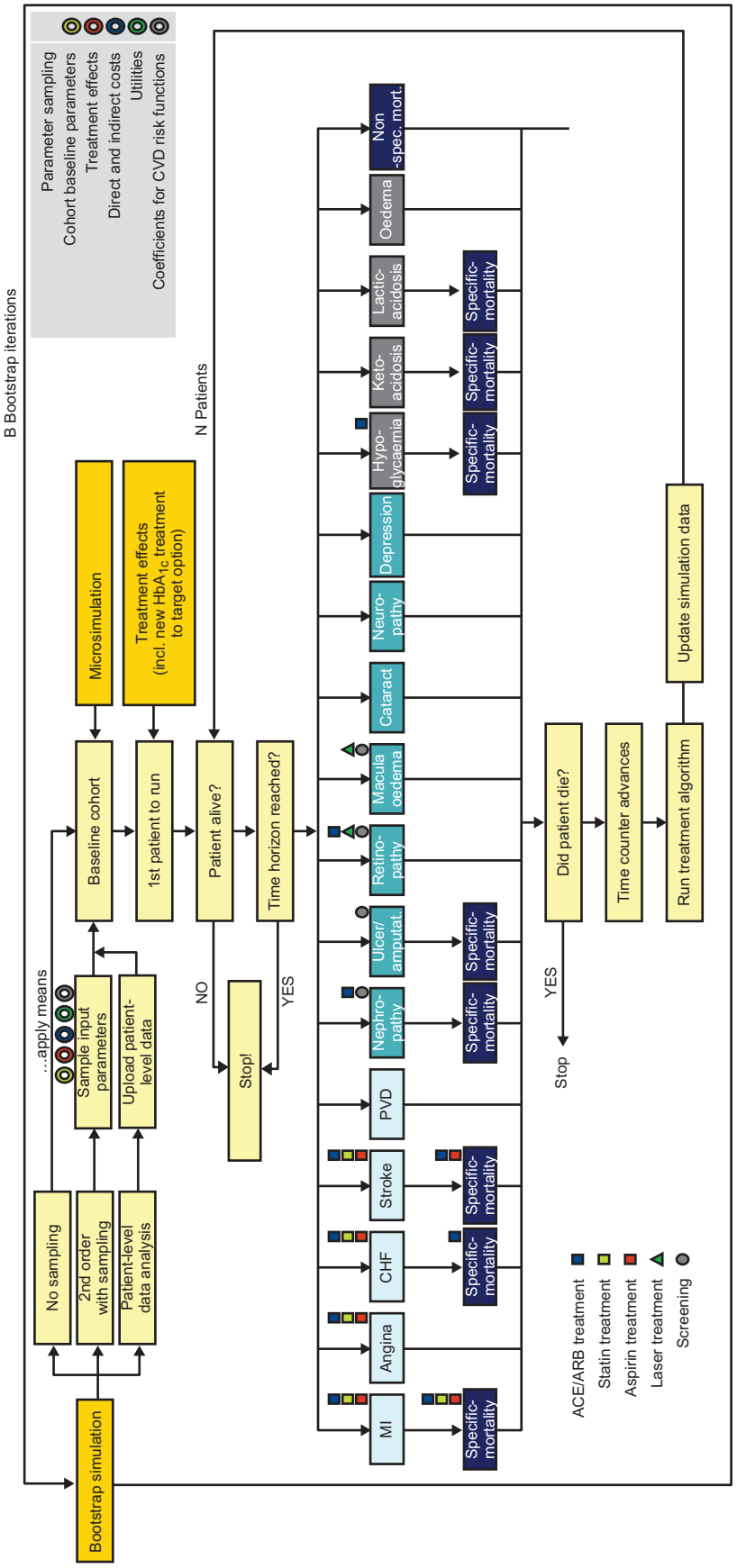
Clinical variables

Baseline characteristics and diabetes history, by type of diabetes, are shown in Table 1 (please see Supplemental table for extended data). Mean (±SD) diabetes duration was 18.2 ± 7.5 years and 16.2 ± 5.0 years for T1D and T2D, respectively. The majority of patients ($n = 48/51$; 94.1%) showed a decrease in HbA_{1c} (Figure 2). HbA_{1c} decreased by a mean of 0.52 ± 0.32%points and 0.68 ± 0.25% points for T1D and T2D, respectively (Table 2). Mean insulin dose increased in T1D (7.1 ± 6.9 U) and T2D (10.7 ± 12.3 U). The mean rate of estimated hypoglycemic episodes per week decreased by > 90% for both T1D and T2D. Weight remained stable in both T1D and T2D.

All T1D patients ($n = 35$) and nearly half ($n = 7$) of patients with T2D changed treatment due to problems with hypoglycemia (e.g., nocturnal hypoglycemia, recurrent hypoglycemia, hypoglycemia while driving) (39/51, 76.5%). Other reasons (sometimes in addition to hypoglycemia) included fear of hypoglycemia (3/51, 5.9%), difficulty or discomfort from injections ($n = 9/51$, 17.6%), excess variability in blood glucose ($n = 6/51$, 11.8%), and flexibility in administration ($n = 8/51$, 15.7%).

Treatment satisfaction

For all six treatment satisfaction and confidence items on the questionnaire, combined mean scores were ≥3.7 (1 = 'much worse', 3 = 'no change', 5 = 'much improved'). The pattern of responses for each of the six individual



ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CHF, congestive heart failure; CVD, cardiovascular disease; MI, myocardial infarction; PVD, peripheral vascular disease.

Figure 1. Overview of the CORE diabetes model structure.

questionnaire items are shown for T1D in Figure 3(a) and for T2D in Figure 3(b).

Health economics

The CDM was initiated with the patient-level data from the chart review for people with T1D. Summary (mean ± SD) profiles are shown in Table 3. Mean (SD) annual insulin cost was £821.6 (£192.8) for insulin glargine/insulin detemir and £1148.9 (£366.3) for insulin degludec. The CDM lifetime analysis showed insulin degludec as dominant (cost savings with additional health benefit) compared with IGlar/IDet; the predicted cost per QALY for insulin degludec vs insulin glargine/insulin detemir was £10,754 when including the effects of hypoglycemia reduction only.

The relationship between observed change in HbA_{1c} following initiation of insulin degludec and projected incremental benefit (QALYs) is shown in Figure 4. A 1% decrease in HbA_{1c} was associated with a 0.65 improvement in discounted benefit ($p < 0.001$). The predicted gain in discounted health benefit associated with the reported percentage reduction in hypoglycemia was non-linear due to differences in baseline frequency (Figure 5). The amount of health benefit ranged from 0.017 QALYs (for a 72% reduction) to 0.057 (for a 99% reduction in hypoglycemia).

Table 1. Baseline demographics of first 51 consecutive patients switching from IDet or IGlar to IDeg in routine clinical practice in the UK.

	T1D ($n = 35$)	T2D ($n = 16$)
Gender (M/F)	15/20	9/7
Age (years)	35.0 ± 11.4	62.8 ± 14.7
Diabetes duration (years)	18.2 ± 7.5	16.2 ± 5.0
Previous basal insulin type (IGlar/IDet)	9/26	1/15
Previous basal insulin (units)	27.7 ± 13.3	76.3 ± 37.5
HbA_{1c}	9.4 ± 0.8	9.4 ± 1.1
Episodes of hypoglycemia per week	3.9 ± 0.9	1.0 ± 1.4
Weight (Kg)	77.0 ± 10.7	102.8 ± 23.0

All values are mean ± SD, unless otherwise specified.

Discussion

This case series is the first to report initial clinical experience with insulin degludec in routine practice including patients experiencing treatment-limiting problems on their previous basal insulin and, as such, provides an illustration of how data derived from clinical practice may be employed to assess the value of the decision to prescribe a new therapeutic entity. The patient group was not selectively chosen but represents the first 51 consecutive patients who were prescribed insulin degludec. Despite the short time frame (mean of 25.5 weeks) reflected by this analysis, there was an overall decrease in HbA_{1c} and clinically important reductions in the frequency of hypoglycemic events. The insulin dose was increased over the course of follow-up, indicating the potential of titrating patients receiving insulin degludec closer to improved glycemic control with a reduced risk of hypoglycemia, which is at variance to the clinical trial data, where there tended to be a reduced basal insulin dose requirement associated with the use of insulin degludec. The data presented within the case series is, however, entirely different in nature to the clinical trial experience with insulin degludec in that there was no randomization, no comparator arm and no pre-specified titration regimen or target. Patients were, however, encouraged to titrate their insulin doses toward a desired fasting plasma of glucose target of 5.5 mmol/l, with hypoglycemia avoidance as a key determinant of the individual patient approach to dose escalation.

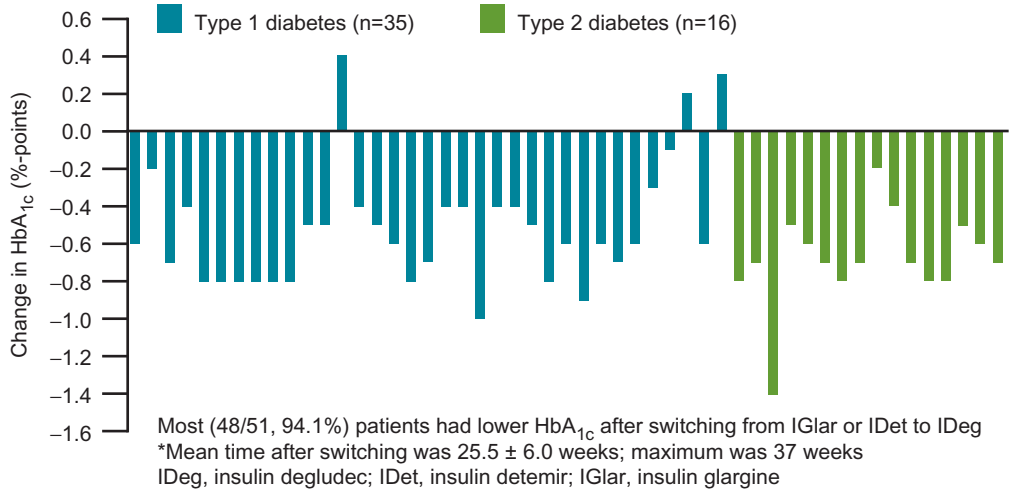


Figure 2. Change from baseline in HbA_{1c} for 51 patients with type 1 or type 2 diabetes following switching to insulin degludec.

Table 2. Mean change in clinical variables after switching to insulin degludec for type 1 ($n = 35$) and type 2 ($n = 16$) diabetes.

	Baseline	Follow-up*	Mean change	Mean difference (%)
HbA_{1c} (% points)				
Type 1	9.4 ± 0.8	8.9 ± 0.9	−0.5 ± 0.3	−5.6
Type 2	9.4 ± 1.1	8.7 ± 1.0	−0.7 ± 0.3	−7.2
Basal insulin dose (U)				
Type 1	27.7 ± 13.3	34.8 ± 18.6	7.1 ± 7.0	27.6
Type 2	76.3 ± 37.5	87.0 ± 43.5	10.7 ± 12.3	14.2
Hypoglycemia (events/week)				
Type 1	3.9 ± 0.9	0.4 ± 0.3	−3.6 ± 0.9	−90.7
Type 2	1.0 ± 1.4	0.08 ± 0.1	−1.0 ± 1.3	−90.3
Weight (kg)				
Type 1	76.2 ± 11.0	77.0 ± 10.7	0.8 ± 1.6	1.1
Type 2	101.5 ± 23.3	102.8 ± 23.0	1.3 ± 1.1	1.4

Data are mean ± SD.
*Mean time after switching was 25.5 ± 6.0 weeks; maximum was 37 weeks.

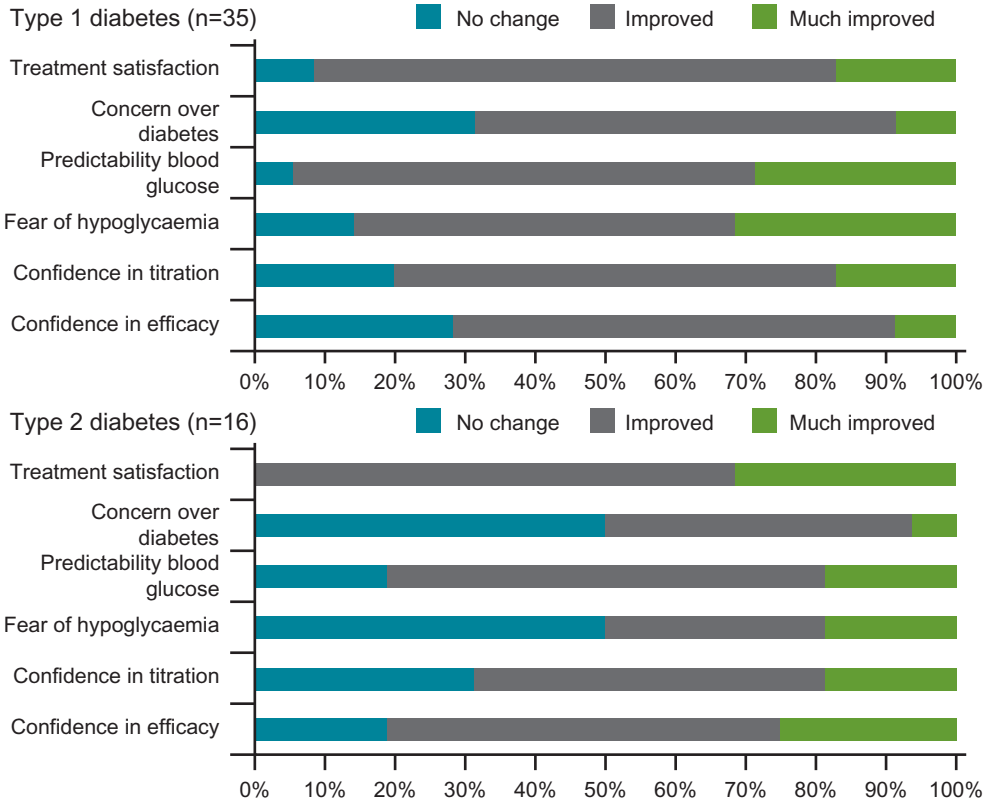


Figure 3. Treatment satisfaction after switching* to insulin degludec, compared to prior basal insulin therapy (insulin detemir or insulin glargine).

However, due to the nature of the patient cohort the mean FPG achieved on self-monitoring in the T1D group was 8.7 mmol/L and 8.3 mmol/L in the T2D group, with no patients consistently achieving fasting self-measured glucose levels <6 mmol/L.

Despite this consideration, the results from this unselected group of patients help establish that the findings from the carefully structured environment of regulatory clinical trials may translate into real-world practice. The observed reduction in hypoglycemia (>90% for both T1D and T2D) in this case series greatly exceeded those reported in a meta-analysis from the clinical trials described earlier (reductions of 17% and 32% for overall confirmed and nocturnal confirmed hypoglycemia,

Table 3. CORE diabetes model analysis for 35 patients with T1D.

35 patients with type 1 diabetes	IGlar/IDet profile	IDeg profile*	CDM lifetime analysis IDeg vs IGlar/IDet
HbA_{1c}	9.4 ± 0.8	8.9 ± 0.9	IDeg was dominant (cost savings with additional health benefit)
Hypoglycemia (events/week)	3.9 ± 0.9	0.4 ± 0.3	Predicted cost per QALY = £10,754
Annual insulin cost	£821.6 (£192.8)	£1148.9 (£366.3)	

Data are mean ± SD.
*Mean time after switching was 25.8 ± 6.0 weeks; maximum was 37 weeks.
CDM, CORE diabetes model; QALY, quality-adjusted life years.

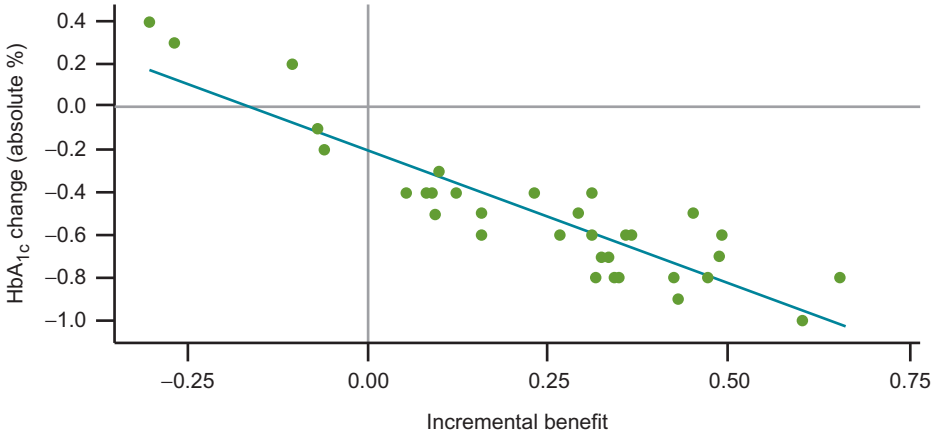


Figure 4. Relationship between observed change in HbA_{1c} after switching* to insulin degludec and projected incremental benefit (quality adjusted life years) in type 1 diabetes ($n = 35$). Each unit decrease in HbA_{1c} was associated with a 0.65 improvement in discounted benefit ($p < 0.001$).

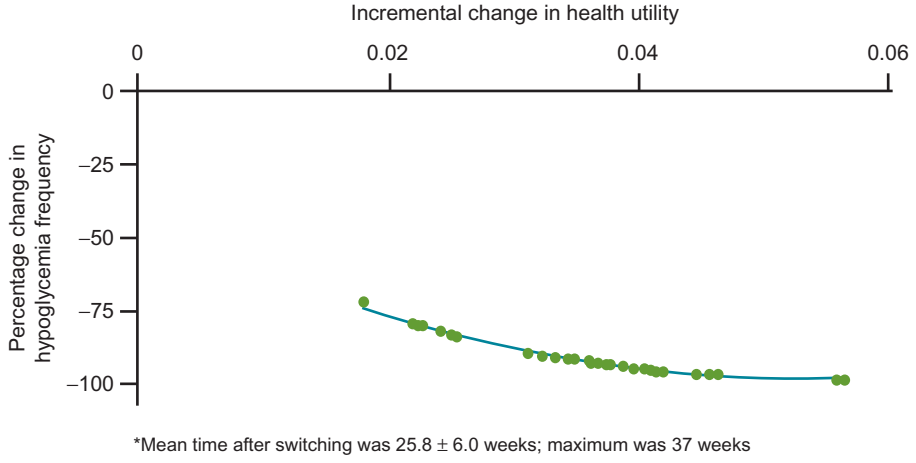


Figure 5. Relationship between the percentage reduction in hypoglycemia frequency and predicted incremental health benefit after switching* to insulin degludec in type 1 diabetes ($n = 35$).

respectively, for insulin degludec vs insulin glargine in T2D, and a reduction of 25% for confirmed nocturnal hypoglycemia in T1D during the maintenance period)[27].

In our group of patients, hypoglycemic events tended to cluster in the first 4–6 weeks following initiation of insulin degludec; subsequent to this initial titration period, the majority of patients experienced very few hypoglycemic episodes. This finding was consistent with the results from the meta-analysis, which reported greater reductions in the hypoglycemia rate ratio for all patient populations during the maintenance period, compared with the titration period of the trials[27].

These improvements in clinical end-points were matched by improvements in patient reported outcomes. The finding of improved measures of treatment satisfaction was consistent with those reported in a meta-analysis of health-related quality-of-life in T2D from trials in the insulin degludec clinical development programme[28]. In that latter analysis, patients completed the validated SF-36 version 2 health survey at baseline and at the end of each trial. The SF-36 questionnaire includes 36 questions distributed across eight scales and two summary measures of physical and mental health calculated from four scales each. The overall physical health component summary score (PCS) was significantly better for insulin degludec compared with insulin glargine (0.66 [0.04–1.28]). Much of that improvement was attributed to improvement in the bodily pain domain score (1.10 [0.22–1.98]), but there was also a significant improvement in the vitality domain score (0.81 [0.01–1.59]). To put those changes in context, a 1-point difference on physical function, bodily pain, or PCS score implies a 2–4% increased risk for hospitalization, 7–12% increase for being unable to work and 4–7% increase for losing the ability to work[37].

The predicted cost per QALY gained for patients with T1D in this study (£10,754) was more than 5-times greater than that reported for patients with T1D in the Swedish analysis (SEK 19,766 or ~£1860)[32]. This greater gain could be because the patients in this study represent a more selected sample, in that patients mostly switched to insulin degludec because of problems with hypoglycemia on their previous basal insulin (insulin detemir or insulin glargine).

This study has a number of limitations. Our study population was a small sample, reflecting the first 51 consecutive patients switching to a new insulin, specifically due to treatment limiting problems on their prior therapy. Therefore, participants may have been more motivated to adhere to optimal diabetes self-management procedures than a randomly selected person with diabetes using insulin. Thus, our observed improvement in clinical parameters cannot be solely attributed to insulin degludec, although initiation of insulin degludec in this group of patients was not associated with any increase in the frequency of self-monitored blood glucose testing as a surrogate marker for adherence with diabetes self-care strategies. Similarly, as with any open label, non-randomized study, participants may also have been more likely to have a more positive opinion of their treatment. Therefore, we would not necessarily expect the same degree of benefit for all patients. Future clinical practice studies would benefit from using a validated instrument, if possible, to measure treatment satisfaction and health-related quality-of-life, as opposed to the generic instrument used in this study. The particular aspects of insulin degludec responsible for the improved satisfaction scores were not recorded in the current study of 51 patients. However, given that many patients switched from their prior insulin due to problems with hypoglycemia or difficulty with their injection regimen, it is likely that the lower incidence of hypoglycemic events and the ability to deliver the entire dose in a single injection with greater flexibility of dose timing (using the U200 formulation) with insulin degludec may be important determinants of the patient experience with this insulin. The improved clinical performance and patient satisfaction scores could also suggest that switching to insulin degludec may result in improved adherence. Although adherence was not measured in this or any other study of insulin degludec reported to date, there are multiple clinical and health-economic outcome benefits arising from improved therapy adherence. Even though the time frame reflected by this analysis was short, the mean period of treatment (25.5 weeks) was similar to that in published randomized trials (i.e., 26 weeks) where both efficacy and safety measures are reported[22,25,38]. Due to the small sample size ($n = 16$), we chose not to explore cost-effectiveness results for patients with T2D. The results of the cost-effectiveness modeling in T1D should be considered as interim findings, given that these results were projected over patient lifetimes. Although there are some cost differences for the 100 U/mL and 200 U/mL formulations, due to the small numbers of patients ($n = 1$ T1D and $n = 8$ T2D) using the 200 U/mL formulation, we were not able to model those costs separately.

Conclusion

These data illustrate the complementary nature of clinical trial and practice data when evaluating the value of therapeutic innovations in diabetes care. In this case series, patients experiencing difficulties such as treatment-limiting hypoglycemia with their current basal insulin regimens who switched to insulin degludec had meaningful reductions in hypoglycemia, along with reduced HbA_{1c} and improved treatment satisfaction. In the sub-sample of people with type 1 diabetes, results suggested that switching to insulin degludec is highly cost-effective and may be cost-saving when its use results in improved blood glucose control coupled with a reduced risk of hypoglycemia. Beyond simply exploring the role of insulin degludec in routine clinical practice, our data, set in the context of ever increasing financial constraints within healthcare systems, provides an insight into the patient phenotype in which the use of insulin degludec may represent the best value for money. As such, this experience may be considered as an exemplar for future clinical practice evaluations to assess the economic and clinical implications of the decision to implement a new technology within any disease area.

Transparency

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Declaration of financial/other relationships
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