The Review of DIABETIC STUDIES

ORIGINAL DATA

3-Month Results from Denmark within the Globally Prospective and Observational Study to Evaluate Insulin Detemir Treatment in Type 1 and Type 2 Diabetes: The PREDICTIVE Study

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■ Abstract

PREDICTIVE™ is a large, multi-national, open-label, prospective, observational study to assess the efficacy and safety of insulin detemir in clinical practice. We report 3-month follow-up data from 389 patients with type 1 (n = 312) and type 2 (n = 77) diabetes from Denmark. Insulin detemir improved glycemic control in type 1 patients, with decreases in mean HbA1c (-0.2%, p = 0.0026), fasting glucose (-1.7 mmol/l, p = 0.0033) and within-patient fasting glucose variability (-0.6 mmol/l, p = 0.0472). Non-significant reductions in glycemic parameters were observed in type 2 patients (-0.3% for HbA1c and -2.7 mmol/l for fasting glucose). There was a decrease in mean body weight in both type 1 and type 2 patients (-0.6 kg, p = 0.025 and -1.0 kg, p = 0.0361, respectively). Three patients (0.8%) reported 4 serious adverse drug reactions, including major hypoglycemia. The incidence of major hypoglycemic episodes was reduced from 3.9/patient-years at baseline to 0.4/patient-years at follow-up in type 1 patients (p < 0.0001), and from 1.0 to 0.0/patient-years in type 2 patients (p = 0.1250). In addition, the mean incidence of total and nocturnal hypoglycemic episodes was reduced in both type 1 (-37.4 and -17.7/patient-years, p < 0.0001 for both) and type 2 patients (-17.7 and -7.8/patient-years, p = 0.0012 and p = 0.0020, respectively). The observations from the Danish cohort of the PREDICTIVE study support the overall findings of PREDICTIVE, i.e. insulin detemir improves glycemic control, with a reduced risk of hypoglycemia and no weight gain.

Keywords: diabetes · insulin analogues · glycemic control · hypoglycemia · diabetes treatment · observational study

Introduction

Diabetes patients have a two- to four-fold increased risk of developing microvascular (renal, neuronal and retinal) and macrovascular complications. Early and intensive intervention in patients with diabetes reduces the risk of these complications and of disease progression [1-3]. Current challenges in diabetes management include strict glycemic control without inducing the undesirable effects of hypoglycemia and weight gain.

In insulin-treated patients, there is a trade-off between glycemic control and hypoglycemia as conventional basal insulins peak after injection and have variable absorption profiles [4]. This can make it difficult to obtain euglycemia. Insulin analogs were designed to

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mimic physiological insulin secretion more closely and have favorably shifted the achievable balance between glycemic control and hypoglycemia. Clinical trials with the basal insulin analog, insulin detemir, have demonstrated a predictable pharmacokinetic and pharmacodynamic profile across patient groups [5-8]. The clinical benefits that have been associated with such a profile include improved and less variable glycemic control in association with reductions in hypoglycemia, in particular nocturnal episodes [9-18]. Clinical trials have also reported that patients benefited from weight loss/neutrality in type 1 diabetes and less weight gain in type 2 diabetes compared with NPH insulin and insulin glargine [9-11, 16-19].

In addition to the clinical trial program PREDICTIVE™ (Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation), a large multinational, observational study, was established to assess the safety and efficacy of insulin detemir in actual clinical practice. The scale of the PREDICTIVE study, which will include more than 30,000 subjects globally, will also provide an opportunity to examine other parameters of diabetes control, such as treatment patterns and glycemic control across countries.

Observational studies are useful in validating clinical trial data [20, 21]. They play an important role in finding out whether the efficacy data from randomized clinical trials, studied under controlled conditions and in selected subjects, translate into an efficacious treatment in routine clinical practice [22]. Additionally, these studies can provide data on adverse effects in a large number of diverse patients [23]. Indeed, the European Agency for the Evaluation of Medicinal Products (EMEA) recognizes the importance of observational studies in monitoring the safety of medicines in clinical practice [24].

As for many countries around the globe, diabetes is already a major health problem in Denmark, and the prevalence of both type 1 and type 2 diabetes is increasing [25, 26]. Glycemic control is slowly improving, but many patients still fail to achieve target levels as defined in management guidelines [27-30].

PREDICTIVE is an open-label, prospective, observational study which aims to evaluate the safety and efficacy of insulin detemir treatment over 12, 26 or 52 weeks (in specific countries) in patients with type 1 or type 2 diabetes. This article provides 12-week follow-up data from type 1 and type 2 diabetes patients initiated on insulin detemir as part of the PREDICTIVE study and discusses the implications of the findings for further improving the management of diabetes in routine clinical practice in Denmark.

Patients and methods

This analysis included 389 men and women with type 1 or type 2 diabetes (80.2% type 1, 19.8% type 2) requiring basal insulin, enrolled at the discretion of their individual physician. Patients were recruited from 28 secondary care sites across Denmark. Details of the main study protocol have been published previously [31]. In brief, the inclusion and exclusion criteria are consistent with the insulin detemir label. Discontinuation of insulin detemir therapy was at the discretion of the physician and was based on clinical evaluation. The study was performed in accordance with Danish regulatory requirements.

Table 1. Baseline demographics

Parameter	T1DM[1] (n = 312)	T2DM[1] (n = 77)
Gender M/F (%)	49.0/51.0	50.6/49.4
Age (yr)	45.6 ± 13.3	61.4 ± 10.9
Diabetes duration (yr)	20.4 ± 12.6	11.8 ± 6.6
BMI (kg/m^2)	24.9 ± 3.6	27.8 ± 5.0
Reasons for insulin detemir[2] (%)		
Reduce risk of hypoglycemia	75	64
Improve glycemic control	44	60
Reduce plasma glucose variability	32	35
Unstable diabetes	28	18
Try new insulin	8	26
Dissatisfaction with current therapy	12	10
Change due to insulin pen	6	14
Improve weight control	2	12
Side effects from current therapy	1	0

Legend: Data for mean age, mean diabetes duration and mean BMI are mean ± SD. T1DM: type 1 diabetes mellitus. T2DM: type 2 diabetes mellitus. M: male. F: female. BMI: body mass index. [1] Efficacy analysis data set; follow-up data unavailable for 158 patients. [2] More than one reason may have been stated.

Baseline demographics, including physicians' reasons for initiating patients on insulin detemir, were collected from patient records and are presented in Table 1. Physicians most frequently commenced insulin detemir treatment to reduce hypoglycemia and to improve glycemic control in both type 1 and type 2 diabetes patients.

Patients were prescribed insulin detemir by their physician, as part of routine clinical care, and followed up for a mean period of 17.1 weeks. The starting dose, administration frequency and subsequent adjustments to treatment regimen were at discretion of the physician.

The majority of type 1 diabetes patients (84%) was treated with basal-bolus insulin therapy prior to the initiation of insulin detemir and at follow-up (87%). Type 2 diabetes patients were primarily receiving oral antidiabetic drugs (OADs) plus insulin (33%) and basal-bolus insulin regimens (39%) prior to the start of the study. The remaining 28% received other types of therapy including basal insulin only, OADs only, bolus insulin only or premix prior to the start of the study. At follow-up, 30% of type 2 patients were receiving OADs plus insulin detemir, 43% basal-bolus insulin therapy with insulin detemir, 10% basal insulin therapy, 1% premix treatment and in 16% the data were missing. The majority of OAD-treated diabetes patients were receiving biguanides at baseline (81%) and follow-up (85%). The proportion of patients using sulphonylureas decreased (22% versus 19%).

The primary and secondary endpoints of the study are shown in Table 2.

Table 2. Primary and secondary study endpoints

Primary endpoint
Incidence of serious adverse drug reactions including major hypoglycemic episodes
Secondary endpoints
Incidence of total and nocturnal hypoglycemia
HbA1c
Mean self-monitored fasting plasma glucose
Within-patient fasting plasma glucose variability [1]
Body weight change

Legend: HbA1c: Hemoglobin A1c. [1] Calculated as the standard deviation of the last two to six fasting glucose measurements.

Safety and efficacy parameters were collected from patient records, recall and patient diaries. Serious adverse drug reactions (SADRs) were recorded for the whole observation period. SADRs were defined as death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect and important medical events that may require medical or surgical intervention. According to the study protocol, a major hypoglycemic episode was to be reported as an SADR and was defined as an episode with symptoms of neuroglycopenia, in which patients were unable to treat themselves, required third party intervention and had plasma blood glucose < 3.1 mmol/l, or in which symptoms regressed after food intake, glucagon or intravenous glucose administration. However, not all major hypoglycemic episodes were reported by investigators as SADRs. We, therefore, describe both major hypoglycemia that was reported by the investigators as a SADR and major hypoglycemia which was not. Hypoglycemic episodes were measured during the 4 weeks before transferring to insulin detemir and again during the 4 weeks before follow-up. Body weight was measured at clinic visits or self-reported by patients. Details on safety and efficacy parameters for the main study population have been reported previously [31].

Statistical analysis

Safety analyses included data from all patients who received at least one dose of insulin detemir. Efficacy analyses included all patients who had a final visit at week 12, at least one dose of insulin detemir and one efficacy measurement at baseline and the final visit, and a follow-up of 8-18 weeks. Demographic characteristics, HbA1c, fasting plasma glucose, body weight, body mass index (BMI) values and hypoglycemic episodes are summarized with descriptive statistics, including mean and standard deviation (SD) for continuous variables and frequency and percentages for categorical variables. Statistical testing was performed using paired t-tests for continuous variables such as HbA1c, weight and mean fasting glucose, and the Wilcoxon paired sign rank sum test for discrete variables, such as incidence of hypoglycemic episodes. A p-value of less than 0.05 was considered statistically significant. Analyses were carried out separately for type 1 and type 2 diabetes patients.

The long-term health economic consequences were analyzed using a peer-reviewed, published Markov model [32, 33]. The clinical observations at baseline and follow-up were projected over a patient's lifetime and compared with life expectancy, quality-adjusted life expectancy and total costs. Danish specific health care costs were applied using a third-party payor perspective (e.g. direct health care costs only). Medication

Table 3. Glycemic control at baseline and after 17 weeks insulin detemir therapy

Glucose control [1]	n	Baseline	Follow-up	Change	p-value
Type 1 diabetes					
Mean HbA1c (%)	181	8.5 ± 1.3	8.3 ± 1.4	-0.2 ± 1.0	0.0026
Mean fasting glucose (mmol/l) [2]	51	9.6 ± 3.7	7.9 ± 1.9	-1.7 ± 3.8	0.0033
Mean within-patient fasting glucose variability (mmol/l)	47	3.4 ± 1.9	2.9 ± 1.4	-0.6 ± 2.0	0.0472
Type 2 diabetes					
Mean HbA1c (%)	39	8.8 ± 1.4	8.5 ± 1.3	-0.3 ± 1.1	0.0643
Mean fasting glucose (mmol/l) [2]	10	10.5 ± 3.4	7.8 ± 2.1	-2.7 ± 3.9	0.0551
Mean within-patient fasting glucose variability (mmol/l)	10	2.9 ± 2.8	1.6 ± 0.8	-1.3 ± 2.3	0.1039

Legend: Data are mean ± SD. [1] Efficacy analysis data set. [2] Fasting blood glucose or fasting plasma glucose, depending on glucose meter.

costs were calculated using the observed doses in the study combined with Danish pharmacy selling prices (excluding value added tax). Cost of test strips and other diabetes-related accessories (glucose meters, lancets, needles etc.) were also included. Because of the relative low number of patients with type 2 diabetes, the health economics analysis was conducted only in type 1 patients.

Results

Of the 389 patients, 42 patients (11%) discontinued the study. The reasons for discontinuation included lost contact (13; 31%), adverse drug reactions (ADRs) (10; 24%), other (17; 40%) and missing (3; 7%). Two reasons for leaving the study were listed for one patient.

Mean HbA1c was significantly lower in type 1 diabetes patients at follow-up compared with baseline (reduction of 0.2%, p = 0.0026, Table 3). A greater decrease of 0.4% was observed in patients with a BMI ≤ 23kg/m^2, while patients with HbA1c levels >9.5% at baseline had a decrease of 0.7% in mean HbA1c at follow-up (Table 4). The number of patients achieving HbA1c target levels (< 7%) increased significantly compared with baseline, from 8.3% to 13.8% in type 1 patients (p = 0.013). An increase of 5.1% to 12.7% in type 2 patients was observed but this was not statistically significant (p = 0.25).

Significant reductions in mean self-monitored fasting plasma glucose (1.7 mmol/l; p = 0.0033) and within-patient fasting plasma glucose variability (0.6 mmol/l, p = 0.0472, Table 3) were also observed in type 1 diabetes patients following insulin detemir therapy. No significant reductions in glycemic parameters were observed in the small number of type 2 diabetes patients (Table 3).

Mean body weight was decreased at follow-up compared with baseline, by 0.6 kg in type 1 (p = 0.025, Figure 1) and 1.0 kg in type 2 patients (p = 0.0361, Figure 1).

Three patients (0.8%) reported 4 SADRs, including major hypoglycemia. Additionally, 5 patients experienced major hypoglycemic episodes that were not reported as SADRs. There were 2 reports of general disorders, which included injection site pain and reaction. A total of 19 patients (5%) reported 28 ADRs, which were mild (61%) or moderate (39%) in severity. Ten patients (3%) had to be withdrawn because of the severity of ADRs. The most common ADRs were local site reactions, which included 10 patients reporting general disorders and administration site conditions, and 6 patients reporting skin and subcutaneous tissue disorders (Table 5).

At follow-up, total hypoglycemic episodes were significantly reduced in both type 1 and type 2 diabetes patients. The mean incidence of total hypoglycemic episodes decreased by 37.4/patient-years in type 1 diabetes patients (p < 0.0001) and by 17.7/patient-years

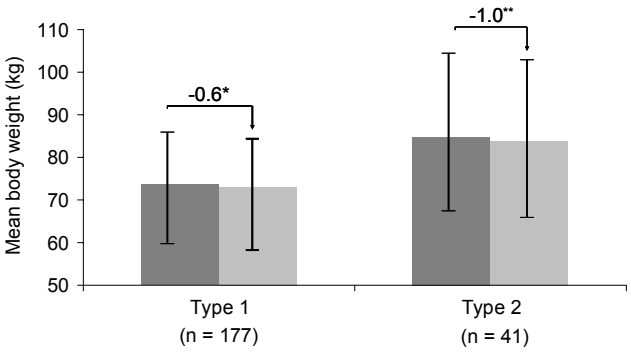

Figure 1. Mean body weight after 17 weeks insulin detemir therapy. ■ Baseline. ■ Follow-up. * p = 0.025, ** p = 0.036.

Table 4. HbA1c change by BMI and HbA1c category in type 1 diabetes patients

Category	n	Absolute change from baseline
BMI		
≤ 23 kg/m²	51	-0.4 ± 1.2
23-25 kg/m²	54	-0.3 ± 0.8
25-27 kg/m²	24	0.0 ± 0.7
> 27 kg/m²	44	-0.1 ± 0.9
Group total	173	-0.2 ± 1.0
HbA1c		
≤ 7.5 %	45	0.2 ± 0.7
7.5-8.5 %	62	-0.2 ± 0.8
8.5-9.5 %	37	-0.3 ± 0.7
> 9.5 %	37	-0.7 ± 1.4
Group total	181	-0.2 ± 1.0

Legend: Data are mean ± SD. BMI: body mass index.

in type 2 diabetes patients ($p = 0.0012$, Figure 2).

Similarly, significant decreases were observed in the mean incidence of nocturnal hypoglycemic episodes. The mean incidence of nocturnal hypoglycemic episodes decreased by 17.7/patient-years in type 1 diabetes patients ($p < 0.0001$) and by 7.8/patient-years in type 2 diabetes patients ($p = 0.0020$, Figure 3). The mean incidence of major hypoglycemic episodes decreased by 3.5/patient-years in type 1 diabetes patients ($p < 0.0001$) and no episodes were reported in type 2 diabetes patients at follow-up ($p = 0.125$, Figure 4).

The mean total dose of insulin remained stable at 0.68 IU/kg at baseline and follow-up in type 1 diabetes patients and increased from 0.59 to 0.64 IU/kg at follow-up in type 2 diabetes patients (Table 6). The basal dose increased by 0.03 IU/kg in type 1 and by 0.04 IU/kg in type 2 diabetes patients (Table 5), while the bolus dose decreased in type 1 and type 2 diabetes patients (-0.02 IU/kg for both, Table 5). Insulin detemir was used once daily in 40% of type 1 and 49% of type 2 diabetes patients and twice daily in 51% of type 1 and 34% of type 2 diabetes patients. Less than 1% of type 1 diabetes patients received 3 or 4 injections of insulin detemir. Data were missing for the remaining patients.

The daily treatment costs were calculated as 43.29 Danish Kroner at baseline and 47.32 Danish Kroner at follow-up in type 1 diabetes patients. The mean life expectancy (undiscounted) was projected to increase at follow-up compared with baseline from 20.3 to 20.6 years. Quality-adjusted life expectancy (discounted at 3% per annum) also increased at follow-up from 6.3 to 8.1 years. The total lifetime costs of treatment were lower at follow-up compared with baseline (535,000 Danish Kroner vs. 569,223 Danish Kroner), primarily because of cost savings on treating major hypoglycemia.

Discussion

The 12-week follow-up data from 389 inadequately controlled type 1 and type 2 diabetes patients in the Danish cohort of the PREDICTIVE study showed that patients benefited from the initiation of insulin detemir therapy.

Table 5. Type and frequency of adverse drug reactions

ADR	n (%)[1]	Number of episodes
General disorders and administration site conditions	10 (2.6)	17
Fatigue		1
Feeling abnormal		2
Injection site erythema		1
Injection site nodule		2
Injection site pain		3
Injection site pruritus		3
Injection site rash		2
Injection site reaction		2
Injection site swelling		1
Musculoskeletal and connective tissue disorders	1 (0.3)	1
Pain in extremity		1
Nervous system disorders	2 (0.5)	2
Dizziness		1
Hypersomnia		1
Skin and subcutaneous tissue disorders	6 (1.5)	7
Eczema		1
Exanthem		1
Generalized erythema		1
Lipohypertrophy		1
Pruritus, generalized		1
Rash		1
Rash, pruritic		1
Uncoded	2 (0.5)	2

Legend: [1] Percentage of total number of patients. Patients may have findings in more than one category.

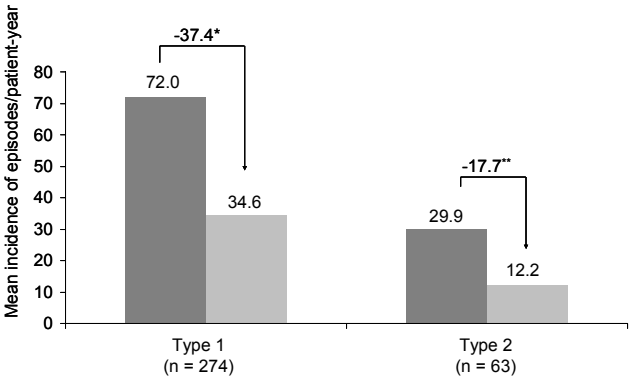

Figure 2. Total hypoglycemia. Hypoglycemic episodes are defined as symptomatic or asymptomatic blood glucose <2.8 mmol/l (50 mg/dl). ■ Baseline: 4 weeks prior to study start. ■ Follow up: 4 weeks prior to follow-up. * $p < 0.0001$. ** $p < 0.0012$.

Glycemic control also improved in type 1 diabetes patients, whereas only a non-significant trend was observed in the small number of type 2 diabetes patients receiving insulin detemir at follow-up. This improvement in glycemic control occurred in conjunction with a significant reduction in weight in both type 1 and type 2 diabetes patients.

There was a significant reduction in the incidence of total and nocturnal hypoglycemia in type 1 and type 2 diabetes patients. Major hypoglycemia was also significantly reduced in type 1 diabetes patients and no episodes were reported in type 2 diabetes patients at follow-up.

A low incidence of ADRs (4.8%) was reported in patients. The most common ADR was local site reactions, but more generalized reactions were also reported. The rate of local site reactions was similar to that observed in patients in clinical practice.

The health economic evaluation reported that the additional medication costs of using insulin detemir therapy were fully offset by reductions in treatment costs, mainly from a reduction in the costs of treating hypoglycemia [32]. The increases in quality-adjusted life expectancy and life expectancy suggest that treatment with insulin detemir may improve quality of life over a patient's lifetime, and that these improvements are not solely a consequence of increased life expectancy [33].

Although observational studies are important in providing data about everyday clinical practice, they have inherent limitations. Caution is therefore needed when drawing conclusions from these results. For example, consideration must be given to the heterogeneity of real-life populations, the lack of standardized treatment regimens and glycemic goals, the absence of a control group and recording safety and efficacy data based on patient recall and diaries. Additionally, the low risk of hypoglycemia reported in the study may be a function of the glycemic control achieved over the study period, which is above levels recommended by consensus guidelines [28-30].

It is of interest, however, that the results from this diverse population are consistent with clinical trial data on insulin detemir [9-14], which report predictable glycemic control, a low risk of hypoglycemia and no weight gain [9-11,16-19]. This indicates that the benefits observed under clinical trial conditions appear to be achievable in routine clinical practice in Denmark. The results are also consistent with the European PREDICTIVE findings [34].

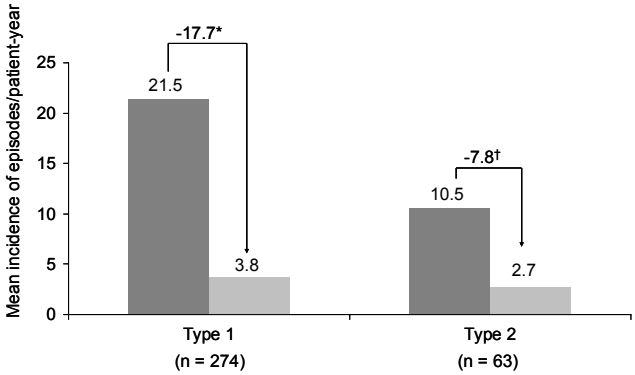

Figure 3. Nocturnal hypoglycemia. ■ Baseline: 4 weeks prior to study start. ■ Follow up: 4 weeks prior to follow-up. * $p < 0.0001$. † $p < 0.002$.

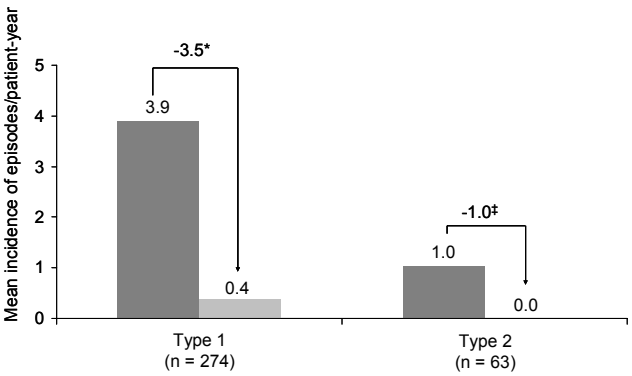

Figure 4. Major hypoglycemia. ■ Baseline: 4 weeks prior to study start. ■ Follow up: 4 weeks prior to follow-up. * $p < 0.0001$. ‡ $p < 0.125$.

Overweight and obesity are common among Danish diabetes patients [25]. In the present study, a weight reduction was reported in both type 1 and type 2 diabetes patients after insulin detemir initiation. This is an interesting finding, as weight gain, a key concern in diabetes patients, is commonly associated with insulin therapy [35, 36]. Clinical trials in patients with type 2 diabetes have shown less weight gain with insulin detemir versus NPH insulin and insulin glargine [16-19]. The reason for the observed weight reduction in this study remains to be elucidated, but it might lead to better compliance and thereby improve glycemic control. Further studies are required to clarify the weight-sparing mechanism of insulin detemir and its clinical impact.

Table 6. Insulin dose at baseline and after 17 weeks insulin detemir therapy

Insulin dose	n	Baseline	Follow-up	Change
Type 1 diabetes				
Mean total	263	0.68 ± 0.23	0.68 ± 0.21	0.00 ± 0.13
Mean basal	242	0.31 ± 0.15	0.34 ± 0.15	0.03 ± 0.10
Mean bolus	240	0.37 ± 0.15	0.35 ± 0.13	-0.02 ± 0.10
Type 2 diabetes				
Mean total	55	0.59 ± 0.26	0.64 ± 0.30	0.05 ± 0.13
Mean basal	50	0.36 ± 0.17	0.40 ± 0.18	0.04 ± 0.12
Mean bolus	33	0.38 ± 0.21	0.36 ± 0.18	-0.02 ± 0.11

The prevalence of diabetes is increasing in Denmark [25, 26], with many patients continuing to fail to reach glycemic control targets [27]. In a study of 2,454 patients from three Danish counties who were regularly monitored, 59% of patients failed to achieve the glycemic treatment target (HbA1c ≤ 6.62%) in 2001 compared with 51% in 2003. Moreover, 75% of patients with 'normal' levels in the first year experienced a subsequent upward trend in HbA1c levels [27]. The findings of this study suggest that this trend, at least in the short term, can be reversed and more patients can achieve guideline targets, which supports a role for insulin detemir in everyday clinical practice in Denmark.

The clinical trial data reported here are consistent with the improved glycemic control and reduced incidence of major hypoglycemia in diabetes patients, which were observed in the type 1 but not type 2 diabetes patients in this cohort. A possible explanation for these results may be the small number of type 2 diabetes patients enrolled and providing efficacy data in the study. Results from the European cohort of the PREDICTIVE study, which includes over 12,900 type 2 diabetes patients, have shown significant improvements in glycemic control and reductions in major hypoglycemia in these patients. For example, in the European cohort, 77% of type 2 diabetes patients achieved good glycemic control with insulin detemir [34].

Additionally, the German subgroup of the PREDICTIVE study showed a greater reduction in HbA1c levels in type 2 diabetes patients [37]. However, in the Danish subgroup there was a tendency towards a greater impact on glycemic control in type 1 diabetes patients in the lower BMI categories, which is in contrast to the findings from the German study.

The effect of insulin detemir on HbA1c levels has also been investigated in other studies. A recent review by Horvath *et al.* analyzed the results of several studies looking at the benefits of insulin detemir and glargine versus NPH insulin [38]. This review reported no clinically relevant difference in HbA1c between treatment groups versus NPH. However, only two studies on insulin detemir were included in this review: the first was not sufficiently powered to show significant differences between detemir and NPH [16], while the second was a treat-to-target study, meaning that both detemir and NPH were titrated to a predefined degree of efficacy and, therefore, likely to give a similar outcome regarding HbA1c [18]. Additional longer term follow-up (26 and 52 weeks) data from the European cohort and other countries in the PREDICTIVE study will indicate whether improved glycemic control, without increased incidence of hypoglycemia or weight gain, can be maintained in a diverse patient population and will provide further insight into the safety and efficacy of insulin detemir in the management of diabetes in clinical practice.

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