

# Insulin detemir improves glycaemic control with less hypoglycaemia and no weight gain in patients with type 2 diabetes who were insulin naive or treated with NPH or insulin glargine: clinical practice experience from a German subgroup of the PREDICTIVE study\*

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**Aim:** The Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) Study is a large, multi-centre, observational study assessing the safety and efficacy of insulin detemir in everyday clinical practice.

**Methods:** This subgroup analysis of the German cohort of PREDICTIVE evaluates over 3 months, patients with type 2 diabetes who were transferred to insulin detemir ± oral antidiabetic drugs (OADs) from an OAD-only regimen (n = 1321), NPH insulin ± OADs (n = 251) or insulin glargine ± OADs (n = 260).

**Results:** Among all groups, 3 months after starting treatment with insulin detemir, total, daytime and nocturnal hypoglycaemic events/patient were reduced by 84, 80 and 90%, respectively, from baseline. No major hypoglycaemic events were reported during treatment with insulin detemir. HbA<sub>1c</sub> was significantly reduced from baseline in each of the subgroups (−1.29, −0.60 and −0.59% for patients previously taking OADs only, NPH insulin ± OADs and insulin glargine ± OADs respectively; p < 0.0001), as was fasting blood glucose (FBG) (−58.1, −29.1 and −24.6 mg/dl; p < 0.0001) and FBG variability (−8.2 mg/dl, −5.7 mg/dl; p < 0.0001 and −5.1 mg/dl; p = 0.0008). All subgroups combined lost an average of 0.9 kg of body weight (p < 0.0001) during the study. Total daily basal insulin dose increased slightly from baseline for those patients on a prior insulin regimen, and in this study 79% of patients used insulin detemir once daily.

**Conclusions:** These data confirm the short-term safety and efficacy of insulin detemir ± OADs in a real-world scenario and support the findings of randomized controlled clinical trials with insulin detemir, including its limited effects on body weight.

Keywords: insulin detemir, insulin glargine, NPH insulin, observational study, type 2 diabetes

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## Introduction

The importance of intensive glycaemic control in reducing the long-term microvascular and macrovascular complications associated with type 2 diabetes has been demonstrated in several landmark clinical trials [1–3]. However, despite recommendations by the American Association of Clinical Endocrinologists [4] and American Diabetes Association (ADA) [5] for more stringent glycaemic goals in patients with diabetes, for example,  $\text{HbA1c} \leq 6.5\%$  and  $\text{HbA1c} < 7\%$ , respectively, the proportion of patients with type 2 diabetes achieving glycaemic control ( $\text{HbA1c} < 7\%$ ) declined from 44.5% in National Health and Nutrition Examination Survey (NHANES) 1988–1994 to 35.8% in NHANES 1999–2000 [6]. Failure to reach glycaemic goals may partly be explained by a delay in initiating insulin therapy, despite failure of oral antidiabetic drugs (OADs). Reasons for delaying insulin include both patient and physician concerns of hypoglycaemia and weight gain, a patient's fear of needles, as well as the view that insulin is the 'last resort' for patients [7]. The 2006 consensus statement from the ADA and European Association for the Study of Diabetes recommends adding a basal (intermediate or long acting) insulin, a sulfonylurea, or glitazone if lifestyle intervention plus metformin fail to maintain a patient's  $\text{HbA1c} < 7\%$  and generally advocates adding a basal insulin to the patient's regimen when OADs are unable to lower  $\text{HbA1c}$  below 7% [8].

Insulin detemir (Levemir, Novo Nordisk, Bagsværd, Denmark) is the latest long-acting, basal insulin analogue to become available for the treatment of diabetes. Insulin detemir is approved for use in adults and children with type 1 diabetes and adults with type 2 diabetes [9,10]. Insulin detemir has been available for use in Europe since March 2004 and was recently launched in the US in March 2006. Insulin detemir has demonstrated effective glycaemic control in several controlled clinical trials in patients with type 1 diabetes on a basal–bolus regimen [11–17], as well in patients with type 2 diabetes, as an add-on to OADs [18,19], and in basal–bolus therapy [20,21]. Further, insulin detemir has demonstrated efficacy similar to Neutral Protamine Hagedorn (NPH) insulin and insulin glargine, but a reduced risk of hypoglycaemia, and in particular, nocturnal hypoglycaemia [11–13,15–18]. The reduced risk of hypoglycaemia associated with the use of insulin detemir has been related to its more consistent pharmacodynamic profile, which translates into more predictable blood glucose levels (less within-patient variability in blood glucose results), compared to both NPH insulin and insulin glargine [22,23]. Interestingly, patients using insulin detemir have also demonstrated

less weight gain compared with those using either NPH insulin [11,12,14,17,18,20,21] or insulin glargine [19].

The Predictable Results and Experience in Diabetes through Intensification and Control to Target: An International Variability Evaluation (PREDICTIVE) Study is a multi-centre, open-label, observational study in patients with type 1 or type 2 diabetes who were transferred to insulin detemir for the management of their blood glucose. The aim of the study is to evaluate the safety and efficacy of insulin detemir under usual practice conditions. In addition, PREDICTIVE provides important insights into different treatment patterns and glycaemic outcomes in several clinical practice settings. As of March 2006, over 30 000 patients in Europe, North America, South America, Africa, Asia and the Middle East have been enrolled in this study.

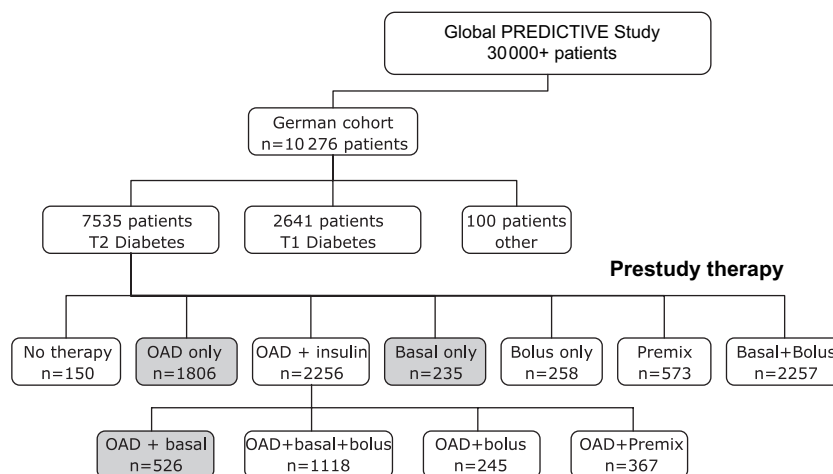
The German cohort of PREDICTIVE has recently completed the study. This publication will present the data on subjects with type 2 diabetes who were judged to need basal-only insulin replacement ( $\pm$ OADs) by their treating physician. Specifically, we present an analysis of three subgroups of patients with type 2 diabetes who transitioned to insulin detemir as the only insulin therapy with or without OADs from the following regimens: OADs only, NPH insulin  $\pm$  OADs and insulin glargine  $\pm$  OADs.

## Methods

Following baseline evaluation, subjects who required basal insulin replacement, as assessed by their treating physician, were eligible for enrolment in the study. Patients were excluded from the trial if they were unlikely to adhere to the protocol, were currently being treated with insulin detemir or had a hypersensitivity to insulin detemir or to any of the excipients. Once started on detemir, changes in insulin dose or OADs during the study period were made, as needed, by the patient's treating physician. While the entire German cohort of PREDICTIVE included 10 276 subjects (2641 and 7535 patients with type 1 and type 2 diabetes, respectively), this analysis focuses on the subgroup of patients with type 2 diabetes whose prestudy regimen was OADs only ( $n = 1321$ ) or basal insulin only  $\pm$  OADs [NPH insulin  $\pm$  OADs ( $n = 251$ ) or insulin glargine  $\pm$  OADs ( $n = 260$ )] (figure 1).

## Study Design and Treatment

This 12-week, open-label, non-randomized observational study was conducted in accordance with the Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects in Germany. The objective of this study was to collect information on the safety and efficacy of



**Fig. 1** Flowchart of patients and their prestudy therapy regimen in the German cohort of the PREDICTIVE study. The 1832 patients in the three subgroups analysed derive from the boxes shaded in grey (OAD only, basal only, OAD + basal) and were transitioned to insulin detemir ± OADs at the beginning of the study. The remaining patients were transitioned to a therapy other than insulin detemir ± OADs.

insulin detemir in normal clinical practice. In Germany, this type of study is regulated by the German Drug Law. Patients volunteered for the study and gave verbal informed consent prior to enrolment (in accordance with local regulations, written consent is not obligatory for observational studies done in Germany, due to the non-interventional design of the study). Physicians also volunteered for the study and received a small compensation for participation.

At the baseline visit the treating physician collected relevant clinical information from patient's recall, notes or logbook and the patient's chart, when available. The medical history included diabetes type and duration, medications, number of total (daytime vs. nocturnal) and major hypoglycaemic events experienced over the preceding 4 weeks, date and result of the most recent HbA1c and the 2–6 most recent fasting blood glucose (FBG) values over the previous 4 weeks. At the final visit, physicians collected the same information as listed above for the 4 weeks that preceded the end of study visit. Severe adverse drug reactions (SADRs), including major hypoglycaemic events and adverse drug reactions (ADRs) were collected over the entire study period.

The treating physician was solely responsible for adjusting the patient's OAD and insulin detemir dose and frequency for the duration of the study. No specific dietary or lifestyle intervention instructions were provided to participants as a part of this study.

### Assessments

The primary objective of this study was to evaluate the short-term safety of insulin detemir under usual practice

conditions in patients needing basal insulin replacement. The incidence of SADRs, including major hypoglycaemic events, during insulin detemir therapy was the main outcome variable in the study. The secondary objective of the study was to evaluate the clinical impact of insulin detemir in a typical clinical setting. Secondary end-points included the number of ADRs, the number of hypoglycaemic events, weight changes, changes in HbA1c, variability in FBG and average FBG. Insulin dose and frequency of injections were also analysed at the end of the study.

HbA1c was measured using standard procedures employed by the clinic the patient attended. The patient's average FBG was calculated from the 2–6 most recent FBG values recorded in the patient's self-monitoring blood glucose diary. Variability was calculated as the s.d. of the patients' 2–6 most recent self-monitored FBG values over the past 4 weeks.

For the purposes of this study, a hypoglycaemic event was defined as an episode with one of the following characteristics: (i) symptoms of hypoglycaemia that resolved with oral carbohydrate intake, glucagon or intravenous glucose, (ii) any symptomatic or asymptomatic blood glucose <50 mg/dl. A nocturnal hypoglycaemic event was defined as an episode consistent with hypoglycaemia that occurred between bedtime (after the evening insulin injection) and before getting up in the morning. A major hypoglycaemic event was defined as an episode with symptoms of neuroglycopenia in which the patient is unable to treat himself/herself and third-party intervention is needed and has one of the following characteristics: (i) blood glucose <50 mg/dl, or (ii) reversal of symptoms after either food intake or glucagon or intravenous glucose administration.

## Statistical Analysis

The analysis of safety outcome variables and data related to antidiabetic therapy were based on the Full Analysis Set (FAS), defined as all patients who received at least one dose of insulin detemir. The analysis of efficacy outcome variables was based on the Efficacy Analysis Set (EAS), defined as all patients from the FAS with at least one efficacy measurement (FBG, HbA1c or weight) at baseline and final visit and with a final visit between 8 and 18 weeks following enrolment.

Statistical testing (comparison before and after insulin detemir therapy) was performed, with paired *t*-tests for continuous variables such as HbA1c, weight or mean FBG and with chi-square statistics for discrete variables, such as incidence of hypoglycaemic events, where available and where appropriate. The McNemar test and the Wilcoxon paired sign rank sum test were performed to compare the percentage of patients with HbA1c < 7% and the number of hypoglycaemic events, respectively, at baseline and at follow-up visit. All testing used two-sided tests with the criteria set at  $\alpha = 0.05$ . Results were interpreted in a descriptive manner; missing data were not replaced.

## Results

The baseline characteristics of the 1832 patients in the FAS and the 1663 patients in the EAS, grouped by their prestudy regimen, are summarized in table 1. The mean age of the study population was  $62.3 \pm 10.6$  years, with a body mass index (BMI) of  $29.8 \pm 5.0$  kg/m<sup>2</sup> and a duration of diabetes of  $7.3 \pm 5.2$  years. As expected, patients already on insulin therapy prior to study enrolment had a slightly longer duration of disease. While at baseline

the group as a whole had a mean HbA1c and FBG of  $8.31 \pm 1.29\%$  and  $176.5 \pm 43.2$  mg/dl, respectively, patients on OADs only had the highest HbA1c and FBG levels. At baseline, 72% of patients were in the OAD only group, while the NPH and insulin glargine groups each made up 14% of the study population. The mean number of daily OADs was 1.7, 1.5 and 1.4 in the OAD-only, NPH and insulin glargine groups respectively (table 2). Metformin and sulfonylureas were the most commonly used oral agents, making up 78% of all OADs used. Of patients taking NPH insulin and insulin glargine prestudy, 63 and 75%, respectively, were also taking OADs.

The most common reasons provided by the treating physicians for starting a patient on, or transferring a patient to, insulin detemir were similar across patient subgroups and included (i) improve glycaemic control (89%), (ii) reduce plasma glucose variability (53%), (iii) patient dissatisfaction with current therapy (33%), and (iv) improve weight control (29%) (table 3).

The mean follow-up time for patients in the entire German cohort of PREDICTIVE was 14.5 weeks with a range of 0–74 weeks. Eleven out of the 1832 (0.6%) patients in this subgroup analysis withdrew from the study. Reasons for patients withdrawing were not reported.

## Safety among the Three Subgroups

Among the 1832 patients in the three subgroups of the German cohort, no SADR were reported during the 3-month follow-up period. Five (0.3% of patients) adverse drug reactions were reported, including one report of drug intolerance, two diabetes-related reports, one report of headache and one report of skin allergy.

**Table 1** Demographic and baseline characteristics

	OADs only	NPH insulin $\pm$ OADs	Insulin glargine $\pm$ OADs	Total
n*	1321	251	260	1832
Age (years)*	$62.2 \pm 10.6$	$61.5 \pm 10.5$	$63.7 \pm 11.1$	$62.3 \pm 10.6$
Gender (female/male) [n (%)]*	653 (49)/668 (51)	123 (49)/128 (51)	138 (53)/122 (47)	914 (50)/918 (50)
Weight (kg (lb))**	$86.3 \pm 15.1$ (189.9 $\pm$ 33.2)	$88.8 \pm 17.0$ (195.4 $\pm$ 37.4)	$86.1 \pm 16.4$ (189.4 $\pm$ 36.1)	$86.5 \pm 15.6$ (190.3 $\pm$ 34.3)
BMI (kg/m <sup>2</sup> )*	$29.5 \pm 4.6$	$30.9 \pm 6.2$	$30.2 \pm 5.1$	$29.8 \pm 5.0$
Duration of type 2 diabetes (years)*	$6.5 \pm 4.7$	$9.0 \pm 5.7$	$9.9 \pm 6.1$	$7.3 \pm 5.2$
HbA1c (%)**	$8.49 \pm 1.29$	$7.82 \pm 1.28$	$7.82 \pm 1.10$	$8.31 \pm 1.29$
FBG (mg/dl)**	$182.9 \pm 42.7$	$159.4 \pm 37.7$	$156.9 \pm 40.5$	$176.5 \pm 43.2$
Within-patient variability in FBG at baseline (mg/dl)**	$20.3 \pm 16.3$	$20.1 \pm 15.1$	$20.1 \pm 17.3$	$20.3 \pm 16.2$

\*Data from full analysis set.

\*\*Data from efficacy analysis set and data for subgroups reported for those patients on QD or BID insulin detemir during the study period; Patient demographics similar between FAS and EAS; Data reported as mean  $\pm$  SD.

**Table 2** OAD therapy at baseline\*

	OADs only	NPH insulin ± OADs	Insulin glargine ± OADs
n	1321	251	260
Number of patients taking at least one OAD (%)	1321 (100)	157 (62.5)	195 (75.0)
Average number of daily OADs**	1.7	1.5	1.4
Number of patients taking $\alpha$ -GLU INH (%)	170 (12.9)	13 (8.3)	13 (6.7)
Number of patients taking SUs (%)	810 (61.3)	59 (37.6)	93 (47.7)
Number of patients taking TZDs (%)	100 (7.6)	7 (4.5)	7 (3.6)
Number of patients taking BIG (%)	971 (73.5)	113 (72)	115 (59.0)
Number of patients taking GLIN (%)	215 (16.3)	37 (23.6)	38 (19.5)

$\alpha$ -GLU INH, alpha-glucosidase inhibitors; BIG, biguanides; GLIN, glinides; SUs, sulfonylureas; TZDs, thiazolidinediones; Data from full analysis set.

\*Missing data not reported.

\*\*Data reported for those patients on QD or BID insulin detemir during the study period.

### Hypoglycaemic events

Major hypoglycaemic events were infrequent among patients within the three subgroups prior to treatment with insulin detemir; 0.1 major hypoglycaemic events per patient year were reported during the 4 weeks preceding the beginning of the study (0.0, 0.4 and 0.3 events per patient year for patients treated with an OAD only regimen, NPH  $\pm$  OADs and insulin glargine  $\pm$  OADs respectively). No major hypoglycaemic events were reported during treatment with insulin detemir.

Both the percentage of patients experiencing hypoglycaemia and the frequency of hypoglycaemic episodes were lower in patients using insulin detemir during the 4 weeks preceding the follow-up visit, compared to baseline (4 weeks prior to the first visit). Baseline total, daytime and nocturnal hypoglycaemic events (3.3, 2.0 and 1.3 events per patient year, respectively) decreased by  $-2.7$ ,  $-1.6$  and  $-1.2$ , respectively ( $p < 0.0001$ ), during the study (figure 2), as did the percentage of patients experiencing these events (7.2, 5.5 and 3.7% at baseline compared to 2.0, 1.6 and 0.5% at follow up).

### Glycaemic Control

#### HbA1c

Overall, a  $1.1 \pm 0.03\%$  ( $p < 0.0001$ ) reduction in mean HbA1c at the end of the study from baseline was

**Table 3** Physician reasons for starting a new therapy\*

	OADs only	NPH insulin ± OADs	Insulin glargine ± OADs	Total
n	1321	251	260	1832
At least one reason* (%)	1319 (100)	249 (99)	259 (100)	1827 (100)
Reason:				
Improve glycaemic control (%)	1224 (93)	207 (83)	206 (79)	1637 (89)
Reduce plasma glucose variability (%)	686 (52)	150 (60)	128 (49)	964 (53)
Patient dissatisfaction with current therapy (%)	415 (31)	85 (34)	100 (39)	600 (33)
Improve weight control (%)	357 (27)	77 (31)	101 (39)	535 (29)
Try new insulin (%)	436 (33)	8 (3)	4 (2)	448 (25)
Unstable diabetes (%)	160 (12)	29 (12)	35 (14)	224 (12)
Reduce risk of hypoglycaemia (%)	64 (5)	39 (16)	34 (13)	137 (8)
Other (%)	66 (5)	17 (7)	20 (8)	103 (6)
Side effects from current therapy (%)	77 (6)	9 (4)	7 (3)	93 (5)
Change due to insulin pen (%)	10 (1)	4 (2)	14 (5)	28 (2)

Data from full analysis set.

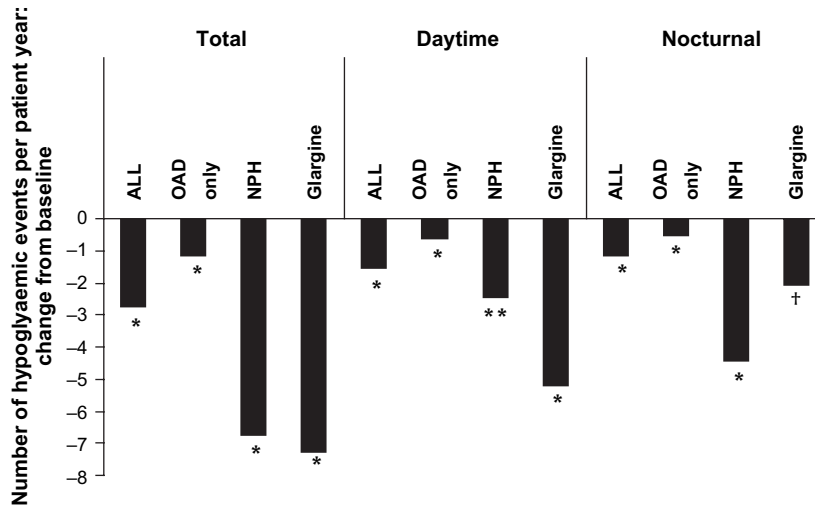
\*A patient may have findings in more than one category.

observed; mean HbA1c at the end of the study was  $7.21 \pm 0.02\%$ . Patients transferred to insulin detemir from an OAD only regimen experienced a decrease in HbA1c of  $1.29 \pm 0.03\%$  ( $p < 0.0001$ ) from baseline, a somewhat greater decrease from baseline than those transitioning from basal insulin regimens (NPH insulin:  $-0.60 \pm 0.09\%$ ; insulin glargine:  $-0.59 \pm 0.06\%$ ;  $p < 0.0001$ ) (figure 3). A greater proportion of overall patients were able to achieve the ADA target HbA1c of less than 7% at study end compared to baseline (42.2% vs. 10.8%;  $p < 0.0001$ ) (figure 4).

#### Fasting blood glucose

A significant reduction in mean FBG was observed among the group as a whole ( $-49.8 \pm 1.1$  mg/dl;  $p < 0.0001$ ). Patients transitioning from an OAD-only regimen tended to have a greater reduction in FBG from baseline ( $-58.1 \pm 1.2$  mg/dl;  $p < 0.0001$ ) than those from NPH  $\pm$  OADs and insulin glargine  $\pm$  OADs regimens ( $-29.1 \pm 3.2$  and  $-24.6 \pm 2.8$  mg/dl respectively;  $p < 0.0001$ ) (table 4).

Compared to baseline, variability in FBG levels was also significantly reduced among the total cohort ( $-7.4 \pm 0.5$  mg/dl;  $p < 0.0001$ ), as well as within each subgroup, transitioning from OADs only ( $-8.2 \pm 0.5$  mg/dl;  $p < 0.0001$ ), NPH  $\pm$  OADs ( $-5.7 \pm 1.1$  mg/dl;  $p < 0.0001$ )

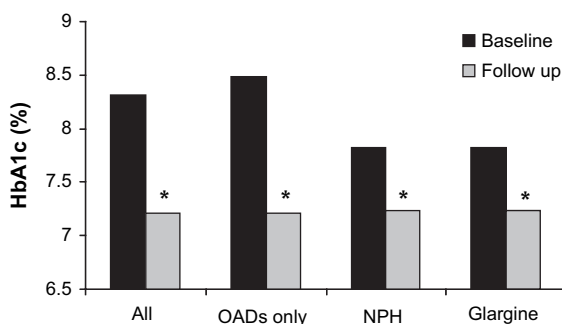


**Fig. 2** Change in the average number of total, daytime and nocturnal hypoglycaemic events per patient year from baseline for all subgroups combined (ALL) ( $n = 1832$ ), as well as each subgroup (patients transitioning from an OAD only regimen ( $n = 1309$ ), NPH insulin  $\pm$  OADs ( $n = 246$ ), insulin glargine  $\pm$  OADs ( $n = 258$ )). Data for each subgroup is from patients on QD or BID insulin detemir. \* $p < 0.0001$ ; \*\* $p = 0.0002$ ; † $p = 0.0007$ .

and insulin glargine  $\pm$  OADs ( $-5.1 \pm 1.5$  mg/dl;  $p = 0.0008$ ) (table 4).

### Weight

Overall, improvements in glycaemic control were accompanied by a  $0.9 \pm 0.1$  kg weight reduction ( $p < 0.0001$ ). Weight reductions of  $0.9 \pm 0.1$  kg ( $p < 0.0001$ ),  $0.9 \pm 0.3$  kg ( $p = 0.0099$ ) and  $0.8 \pm 0.2$  kg ( $p < 0.0001$ ) were observed in those patients transitioning from OAD only, NPH  $\pm$  OADs, and insulin glargine  $\pm$  OAD regimens respectively (table 4).

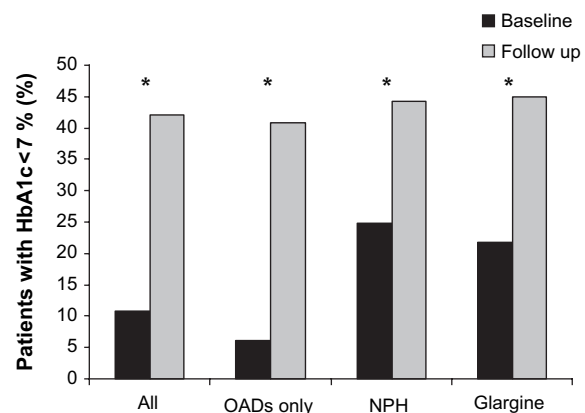


**Fig. 3** HbA1c at baseline and at follow-up visit for all subgroups combined (ALL) ( $n = 1556$ ), as well as each subgroup [patients transitioning from an OAD only regimen ( $n = 1116$ ), NPH insulin  $\pm$  OADs ( $n = 206$ ), insulin glargine  $\pm$  OADs ( $n = 216$ )]. Data for each subgroup is from patients on QD or BID insulin detemir. \* $p < 0.0001$  (change from baseline). Missing data not replaced.

### Insulin Dosing and OAD Regimen

Given the option of once- (QD) or twice-daily (BID) dosing, most providers placed their patients on QD insulin detemir (79% of patients). There were no apparent differences in gender, age, weight, BMI or duration of diabetes between the groups of patients on QD and BID insulin detemir.

Among those patients transitioning from NPH insulin and insulin glargine, the average daily dose of insulin



**Fig. 4** Percentage of patients with HbA1c < 7% at baseline and at follow-up visit for all subgroups combined (ALL) ( $n = 1558$ ), as well as each subgroup [patients transitioning from an OAD only regimen ( $n = 1118$ ), NPH insulin  $\pm$  OADs ( $n = 206$ ), insulin glargine  $\pm$  OADs ( $n = 216$ )]. Data for each subgroup is from patients on QD or BID insulin detemir. \* $p < 0.0001$  (comparison of baseline and follow up).

**Table 4** Data at final visit

	OADs only‡	NPH insulin ± OADs‡	Insulin glargine ± OADs‡	Total
n	1116	206	216	1556
HbA1c at follow up (%)	7.21 ± 0.03	7.23 ± 0.07	7.23 ± 0.06	7.21 ± 0.02
Change in HbA1c from baseline (%)	-1.29 ± 0.03*	-0.60 ± 0.09*	-0.59 ± 0.06*	-1.10 ± 0.03*
n	1001	170	184	1368
FBG at follow up (mg/dL)	124.8 ± 0.8	130.2 ± 2.8	132.3 ± 2.2	126.7 ± 0.7
Change in FBG (mg/dL)	-58.1 ± 1.2*	-29.1 ± 3.2*	-24.6 ± 2.8*	-49.8 ± 1.1*
n	794	148	155	1108
Within-patient variability at follow up (mg/dl)	12.1 ± 0.3	14.4 ± 0.9	15.0 ± 1.0	12.9 ± 0.3
Change in within-patient variability (mg/dl)	-8.2 ± 0.5*	-5.7 ± 1.1*	-5.1 ± 1.5**	-7.4 ± 0.5*
n	1174	213	222	1627
Weight in kg at follow up (lb)	85.4 ± 0.4 (187.9 ± 0.9)	87.9 ± 1.1 (193.4 ± 2.4)	85.3 ± 1.1 (187.7 ± 2.4)	85.6 ± 0.4 (188.3 ± 0.9)
Change in weight in kg (lb)	-0.9 ± 0.1 (-2.0 ± 0.2)*	-0.9 ± 0.3 (-2.0 ± 0.7)†	-0.8 ± 0.2 (-1.8 ± 0.4)*	-0.9 ± 0.1 (-2.0 ± 0.2)*

Data from efficacy analysis set.

\* $p < 0.0001$ .

\*\* $p = 0.0008$ .

† $p = 0.0099$ .

‡Data reported for those patients on QD or BID insulin detemir during the study period; Data reported as mean ± SE.

detemir at the patient's final visit was slightly higher than the patient's pretrial dose of NPH insulin [27.2 U (0.31 U/kg) vs. 25.3 IU (0.29 IU/kg);  $p = 0.0114$ ] and insulin glargine [27.1 U (0.32 U/kg) vs. 23.6 IU (0.27 IU/kg);  $p < 0.0001$ ] (table 5). The average daily dose of insulin detemir at follow up for patients who transitioned from an OAD only regimen was 18.8 U (0.22 U/kg).

On average, insulin dose adjustments were made 2.2 times during the study period, with 19% of patients requiring no dose adjustment. The majority of patients (~65–70%) within each subgroup adjusted their insulin detemir dose twice or fewer numbers of times during the study period. At the end of the study period, 94% of patients were continued on insulin detemir.

OAD use among patients transitioning from an OAD-only regimen tended to decrease from baseline (table 2) to follow up; specifically, a smaller percentage of patients within this subgroup were taking alpha-glucosidase inhibitors, sulfonylureas and thiazolidinediones (TZDs) at follow up compared to baseline. However, overall the OAD regimens of patients within each subgroup did not change substantially from baseline to follow up.

## Discussion

Basal insulin replacement is an effective treatment for lowering glycaemia in patients with type 2 diabetes not adequately controlled on oral agents alone [8]; however, the risk of hypoglycaemia and concerns of weight gain are some of the barriers to initiating insulin therapy and

achieving ideal glycaemic control. While insulin detemir has been evaluated extensively in controlled clinical studies with more than 6000 patients with diabetes, this sub-analysis of the German cohort of the PREDICTIVE study provides new and interesting insights into the use of insulin detemir as basal-only insulin replacement in patients with type 2 diabetes in a real-world medical practice setting, and focuses on the short-term safety and effectiveness of this novel basal analogue.

**Table 5** Insulin detemir dose at baseline and follow up

	OADs only**	NPH insulin ± OADs**	Insulin glargine ± OADs**	Total*
n	1309	246	258	511
Total daily basal insulin dose [IU (IU/kg)] at baseline	n/a	25.33 (0.29)	23.63 (0.27)	24.54 (0.28)
Total daily basal insulin dose [U (U/kg)] at follow up	18.75 (0.22)	27.19 (0.31)††	27.09 (0.32)†	27.40 (0.32)†

n/a, not applicable. Data from full analysis set.

\*Includes only data from patients transitioning from NPH ± OADs and insulin glargine ± OADs

\*\*Data reported for those patients on QD or BID insulin detemir during the study period.

† $p < 0.0001$ .

†† $p = 0.0114$  (change from baseline).

## Summary of Data and How They Relate to Clinical Trial Results

The results presented in this sub-analysis of the German cohort of the PREDICTIVE study support and confirm some of the key observations from prior clinical studies with insulin detemir. Although the finding of improved glycaemic control when insulin detemir was added to OADs is expected, and could in part be due to a study-related effect, we are aware of no studies that demonstrate this level of improvement in glycaemic control (HbA1c – 1.3% compared to baseline) when basal insulin is added to insulin-naïve subjects along with a concomitant reduction in both weight and hypoglycaemia frequency (both statistically significant). The combination of these three observations in this clinical setting cannot be merely dismissed as solely due to a study-related placebo effect, but must be carefully considered alongside results from randomized controlled trials with insulin detemir.

Clinical studies comparing insulin detemir with NPH insulin in patients with type 2 diabetes have consistently shown less weight gain [18,20,21], less variation in FBG levels [20,21] and a lower risk of hypoglycaemia [18] with insulin detemir. Similarly, some trials comparing insulin glargine with insulin detemir in type 1 and type 2 diabetes have demonstrated a lower risk of major and nocturnal hypoglycaemia [15] and less weight gain [19], respectively, with insulin detemir, while achieving similar reductions in HbA1c. The concomitant findings of reduced hypoglycaemia, improved glycaemic control, less variability in FBG and a small weight loss from baseline in this sub-group analysis again confirm results from prior clinical trials and cannot be attributed solely to a study-related effect.

Similar to its use in the USA, metformin was the most commonly used OAD, both in insulin-naïve patients, as well as those on basal insulin therapy. In contrast to typical practice in the USA, TZD use was relatively low in patients both before and during the study, due to its labelling restrictions in Europe.

The improvement in glycaemic parameters observed in this study are not unexpected, given that the most common reason for a physician to start his or her patient on insulin detemir was to improve glycaemic control. To this purpose physicians may have been more aggressive in pursuing glycaemic targets and by the end of the study were using somewhat higher doses (~3 units) of insulin detemir. Improved glycaemic outcomes may have further been a result of safer adjustments of insulin doses, given the lower frequency of hypoglycaemia and more consistent glucose profiles.

As with previous clinical trials using insulin detemir, the outcome of improved glycaemic control with reduced hypoglycaemia and less weight gain was clearly evident in this short-term observational study. The reduced incidence of hypoglycaemic events with insulin detemir has been related to its more consistent blood glucose response [22] likely due, in part, to insulin detemir's mechanism of action [24]. The mechanism behind insulin detemir's favourable weight effects are still under investigation. Pre-clinical studies have suggested that insulin detemir's mechanism of action may also play a role in reducing weight gain by exhibiting greater effects in the liver as opposed to the periphery [25] and by displaying enhanced activity in the brain, which may act to suppress appetite [26]. Both hypothetical mechanisms are in line with a restoration of a more physiological mode of insulin action. A reduction in hypoglycaemic events may also contribute to less weight gain, as patients are less likely to resort to defensive or corrective snacking to combat hypoglycaemia; however, no correlations between weight gain and hypoglycaemia were found in one clinical study [27].

### *Feasibility of treatment with insulin detemir*

Basal insulin therapy is commonly used to initiate insulin in, as well as treat patients with type 2 diabetes whose glycaemia is inadequately controlled on diet/exercise and OADs. Several clinical trials have demonstrated the efficacy and safety of a basal insulin regimen [18,28,29]. Clinical trial data with insulin detemir have demonstrated its efficacy in a once- or twice-daily regimen. In this study, nearly 80% of patients used insulin detemir once daily and achieved significant reductions in HbA1c, FBG and FBG variability, while experiencing a reduction in total, daytime and nocturnal hypoglycaemic events from their baseline regimen. Moreover, insulin doses were adjusted an average of 2.2 times during the study period, with no clinically relevant changes in insulin dose from prior insulin regimens and almost 20% of patients remaining on the same dose of insulin detemir.

### *The importance of predictability in type 2 diabetes*

The more consistent blood glucose response observed with insulin detemir likely has clinical, as well as psychological implications for the patient and physician. Less variability in FBG levels translates to less likelihood of experiencing hypo- and hyperglycaemia [22]. Furthermore, reduced variability in FBG levels may allow more timely titration of basal insulin, with less fear of hypoglycaemia, especially nocturnal hypoglycaemia.

### Limitations of observational data

Observational studies like PREDICTIVE are a relatively straightforward means to gain important safety and efficacy information on new therapies, while confirming in a real-world setting outcomes observed in clinical trials [30]. However, this study has several limitations that need to be discussed. Firstly, this is a short-term study, and the favourable clinical benefits observed in this trial following the administration of insulin detemir may not necessarily be maintained over a longer period of observation. A longer-term follow up would be needed to ensure continued glycaemic and metabolic benefits. Results from such studies can be challenging to analyse and interpret because of the heterogeneity of real-life populations, the lack of standardized treatment regimens, the lack of pre-defined end-points and, importantly, the absence of a control group [31]. Despite these challenges we feel that the results of this study should be reproducible in the vast majority of patients with type 2 diabetes having similar characteristics to this study population. The small differences in weight (BMI) between this European cohort and the usual North American subject with type 2 diabetes is not expected to have a substantial impact on the general findings of this study, except perhaps for the need of somewhat larger insulin dose requirements. However, we cannot exclude that some of the improvements in glycaemia, weight and hypoglycaemia frequency might have been study-related effects, although we would be hard pressed to ascribe all of these findings to this phenomenon. Dismissing the observed outcomes in the insulin naïve cohort on the basis of study effect would have no precedence in the medical literature. The fact that 12-week data from this sub-analysis of the German cohort of the PREDICTIVE study are consistent with findings observed in controlled clinical trials is encouraging and corroborates the clinical trial data collected for insulin detemir thus far.

### Conclusion

This report from the German cohort of the PREDICTIVE study provides the first confirmation in everyday clinical practice that insulin detemir's short-term safety and efficacy are consistent with findings from earlier clinical trials. Furthermore, this subgroup analysis suggests that patients with type 2 diabetes who transfer to a once-daily regimen with insulin detemir from a regimen of OADs only, or a basal insulin regimen, can experience improved glycaemic control with less hypoglycaemia and no weight gain. The applicability of the data to a global setting will become more apparent as results from additional cohorts

of the PREDICTIVE study begin to emerge over the next year. Taken together, these studies will help to provide a more complete picture of the real-world use of insulin detemir, as well as insights into practice patterns in the treatment of diabetes around the world.

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