Insulin detemir improves glycaemic control without weight gain in insulin-naïve patients with type 2 diabetes: subgroup analysis from the PREDICTIVE™ study

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SUMMARY

Objective: Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE™) is a multi-national, open-label, prospective, observational study assessing the safety and efficacy of insulin detemir in clinical practice. This post hoc subanalysis evaluates insulin-naïve patients on oral antidiabetic drugs (OADs) who were initiated on insulin detemir as basal therapy (± OADs). Methods: The European cohort of the PREDICTIVE study currently includes 20,531 patients (12,981 with type 2 diabetes) who were prescribed insulin detemir and followed up for 12, 26 or 52 weeks. Here, we report data from a subgroup of 2377 OAD-treated, insulin-naïve type 2 diabetes patients for a mean follow-up of 14.4 weeks. Patients were prescribed insulin detemir as basal therapy (± OADs) by their physician, as part of routine clinical care. Results were reported in comparison with baseline observations.

Results: One serious adverse drug reaction was reported, which was a major hypoglycaemic episode. Treatment with insulin detemir (± OADs) significantly reduced mean haemoglobin A1c (HbA1c) (1.3%; p < 0.0001), fasting glucose (−3.7 mmol/l; p < 0.0001), and within-patient fasting glucose variability (−0.5 mmol/l; p < 0.0001). In the majority of patients (82%), these improvements in glycaemic control were achieved with once daily administration of insulin detemir. There was a small reduction in mean body weight (−0.7 kg; p < 0.0001), which was most apparent in patients with a higher body mass index (BMI) at baseline. A significant negative relationship between weight change and baseline BMI was observed (greater the BMI, greater the weight reduction). Multiple regression analysis showed that BMI and HbA1c, at baseline, and change in HbA1c, were all predictors for weight change (p < 0.0001 for all), with BMI being the strongest predictor.

Conclusions: Patients with type 2 diabetes naïve to insulin can be effectively treated with once-daily insulin detemir (± OADs) to achieve improved glycaemic control with no adverse effect on weight and a low risk of hypoglycaemia. These short-term results are consistent with the findings of clinical trials.

Introduction

The management of type 2 diabetes has traditionally followed a stepwise approach, in which failure to achieve optimal glycaemic control through lifestyle modifications necessitates the introduction of more intensive treatment strategies with oral antidiabetic drugs (OADs) and insulin (1,2).

The timely initiation of insulin helps to improve glycaemic control (3), which is important in preventing the chronic complications of diabetes (4,5). Additionally, timely initiation of insulin therapy may protect beta cells from further functional impairment caused by extended exposure to hyperglycaemia (6,7). Current consensus American and European treatment guidelines recommend the addition of insulin therapy to lifestyle intervention strategies and metformin therapy in patients with a haemoglobin A1c (HbA1c) level > 7.0% (8).

Despite the efficacy of insulin therapy in type 2 diabetes, there is a disparity between guidelines and clinical practice with regard to timely initiation (9).
The reluctance of physicians and patients to initiate insulin therapy can contribute to periods of poor glycaemic control in individuals with type 2 diabetes, ultimately increasing the risk of micro- and macrovascular complications. Recognised barriers to insulin initiation include patient and physician concerns about weight gain and hypoglycaemia (2,3,10), and patient fear of injections (3,11).

The newly introduced insulin analogues help patients and physicians overcome these barriers. Clinical trials in insulin-naive type 2 diabetes have shown that a very simple approach of adding a basal insulin analogue to a current OAD regimen can improve glycaemic control with a reduced frequency of hypoglycaemia (12,13). While the pharmacokinetic and pharmacodynamic profile of the two basal insulin analogues, insulin glargine and insulin detemir, have been shown to be similar (14), the latter has been shown to exhibit a reduced variability in time-action profile (15). With insulin detemir, the improvement in glycaemic control following insulin initiation was achieved with less weight gain compared with neutral protamine Hagedorn (NPH) insulin and insulin glargine (12,16).

Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE™, Novo Nordisk A/S, Bagsvaerd, Denmark) is a large, multi-national, observational study to assess the safety and efficacy of insulin detemir in actual clinical practice. Follow-up data from the European cohort of the PREDICTIVE study have been reported previously (17).

The study has a large cohort of patients who were insulin naive and were initiated on insulin detemir (± OADs) and provides us a first-time opportunity to evaluate the response of patients to this approach to insulin initiation in actual clinical practice setting in Europe.

**Fig. 1** Treatment regimen of type 2 diabetes patients enrolled in 11 countries from the European cohort. OAD, oral antidiabetic drug. Shaded area indicates study group.
Changes in insulin regimen, insulin dose and to OAD treatment were at the discretion of their individual physician. Discontinuation of insulin detemir therapy was at the discretion of the physician, and was based on clinical evaluation. Inclusion and exclusion criteria have been reported previously (18).

**Primary and secondary end-points**

The primary end-point was incidence of serious adverse drug reactions (SADRs), including major hypoglycaemia. Hypoglycaemia was defined as an event with one of the following characteristics: symptoms of hypoglycaemia that resolve with oral carbohydrate intake, glucagon or intravenous glucose, or any symptomatic or asymptomatic blood glucose < 50 g/dl (2.8 mmol/l). A nocturnal hypoglycaemic event was defined as individualised symptomatic events consistent with hypoglycaemia, that occur while the subject is asleep, between bedtime (after the evening insulin injection) and before getting up in the morning (before morning determination of fasting blood glucose and morning injection). Major hypoglycaemia was defined as an episode with symptoms of neuroglycopenia, in which the patient was unable to treat himself/herself and third party intervention was needed, and the patient had a blood glucose < 2.8 mmol/l or reversal of symptoms after food intake, glucagon or intravenous glucose administration. Secondary end-points included: HbA1c, mean self-monitored fasting glucose within-patient fasting glucose variability [calculated as the standard deviation (SD) of the last two to six fasting glucose measurements]; number of total and nocturnal hypoglycaemic episodes; and change in body weight.

Safety and efficacy parameters were collected from patient records, recall and patient diaries. SADRs were recorded for the whole observation period. The incidence of hypoglycaemic episodes was measured at 4 weeks before starting insulin detemir and again in the 4 weeks prior to follow-up. Weight was measured at the clinic or self-reported by patients. Details on safety and efficacy parameters for the main study population have been reported previously (18).

**Statistical analysis**

Safety analyses included data from all patients who received at least one dose of insulin detemir. Efficacy analyses included data from all patients who received at least one dose of insulin detemir and had at least one efficacy measurement at baseline and during weeks 8–18 of the follow-up period. Demographic characteristics, HbA1c, fasting glucose, body weight, body mass index (BMI) values, and hypoglycaemic episodes are summarised with descriptive statistics, including mean and SD for continuous variables, and frequency and percentages for categorical variables. A subanalysis was performed according to different baseline BMI categories (< 25, 25 to < 27, 27 to < 29, 29 to < 31 and ≥ 31 kg/m²) to explore changes in HbA1c, insulin dose, and weight (13). Multiple regression analysis was conducted to determine the relationship between change in body weight and baseline HbA1c, BMI, change in HbA1c and insulin dose at follow-up. Statistical testing was performed using paired t-tests for continuous variables such as HbA1c, weight, and mean fasting glucose, and Wilcoxon pairwise sign rank sum test for discrete variables, such as incidence of hypoglycaemic episodes. A p-value of < 0.05 was considered statistically significant.

**Results**

**SADRs and hypoglycaemia**

A detailed description of the SADRs for the European cohort has been reported previously (17). In this subgroup of insulin-naïve type 2 diabetes patients initiated on insulin detemir (± OADs), one SADR was reported in the 4 weeks prior to the baseline visit, which was a major hypoglycaemic episode.

The incidence of total, major and nocturnal hypoglycaemic episodes was low in the 4 weeks prior to baseline and did not increase in the 4 weeks prior to the follow-up visit (Figure 2).

**Glycaemic control and insulin dose**

Significant improvements in glycaemic control were observed at 14 weeks after initiating insulin detemir therapy. Mean HbA1c was reduced from 8.9% to 7.6% (−1.3%; p < 0.0001; Table 2). Significant

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**Table 1** Baseline demographics of OAD-treated, insulin-naïve type 2 diabetes patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Type 2 (n = 2377)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender M/F, % patients</td>
<td>48/52</td>
</tr>
<tr>
<td>Mean age, years ± SD</td>
<td>60.3 ± 10.9</td>
</tr>
<tr>
<td>Mean diabetes duration, years ± SD</td>
<td>7.9 ± 5.8</td>
</tr>
<tr>
<td>Mean BMI, kg/m² ± SD</td>
<td>29.5 ± 4.9</td>
</tr>
</tbody>
</table>

BMI, body mass index; OAD, oral antidiabetic drug; SD, standard deviation.
reductions were also observed in mean fasting glucose and mean within-patient fasting glucose variability (-3.7 and -0.5 mmol/l respectively; p < 0.0001 for both; Table 2). When the data were analysed according to BMI category, the results for HbA1c were consistent within the whole subgroup (Table 2).

The majority of OAD-treated type 2 diabetes patients were receiving biguanides at baseline (73%) and follow-up (71%). The proportion of patients using sulphonylureas, thiazolidinediones and alpha-glucosidase inhibitors decreased (72% vs. 46%, 13% vs. 8% and 13% vs. 5% respectively). Of the OAD-treated patients who were initiated on insulin detemir as basal therapy, 14% had their OADs discontinued and were receiving insulin detemir monotherapy at the follow-up visit. At follow-up, the mean daily amount of basal insulin was 22 U, and 82% of all patients were on one injection daily.

Body weight
A statistically significant decrease in mean body weight (~0.7 kg; p < 0.0001) was observed following insulin detemir therapy (± OADs). A large proportion of patients (68%) gained no weight or experienced weight reduction during 14 weeks of insulin detemir therapy (Figure 3). Thirteen per cent of patients achieved a weight loss of > 3 kg at follow-up. When weight change was analysed by baseline BMI, patients with a BMI < 25 kg/m² gained a small amount of weight (0.55 kg), while patients with a BMI ≥ 25 kg/m² experienced weight reduction that was proportional to baseline BMI (Figure 4). Those patients in the BMI ≥ 31 kg/m² category had the greatest reduction in weight (1.5 kg). Regression analysis revealed a statistically significant negative relationship between weight change and BMI (p < 0.0001; Figure 5). HbA1c at baseline and change in HbA1c were positively associated with weight change (p < 0.0001 for both). Of these parameters, BMI was the strongest predictor of weight change in this group of patients newly initiated on insulin detemir.

Discussion
The addition of basal insulin to OADs is an effective insulin initiation option. Early studies with NPH insulin reported that one injection of bedtime insulin in combination with metformin provides effective glucose lowering, with minimal risk of hypoglycaemia and weight gain (19,20). The introduction of

![Figure 2](image-url) Mean incidence of total, major and nocturnal hypoglycaemic episodes at baseline and at follow-up in oral antidiabetic drug (OAD)-treated, insulin-naive patients who were initiated on insulin detemir (± OADs; n = 2375)

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Efficacy measures following 14 weeks insulin detemir treatment (± OADs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Glucose control*</td>
<td></td>
</tr>
<tr>
<td>Mean HbA1c, % ± SD</td>
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<tr>
<td>Mean self-monitored fasting glucose†, mmol/l ± SD</td>
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</tr>
<tr>
<td>Mean within-patient variability, mmol/l ± SD</td>
<td>1212</td>
</tr>
<tr>
<td>Body weight*</td>
<td></td>
</tr>
<tr>
<td>Mean body weight, kg ± SD</td>
<td>2023</td>
</tr>
<tr>
<td>Mean HbA1c by BMI category, kg/m² ± SD*</td>
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</tr>
<tr>
<td>&lt; 25</td>
<td>225</td>
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<tr>
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<tr>
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<tr>
<td>29 to &lt; 31</td>
<td>306</td>
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<tr>
<td>≥ 31</td>
<td>580</td>
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*Efficacy analysis data set (see text for details). †Fasting blood glucose or fasting plasma glucose, depending on glucose meter used. BMI, body mass index; 95% CI, 95% confidence interval for mean change; HbA1c, haemoglobin A1c; OAD, oral antidiabetic drug; SD, standard deviation.
Figure 3  Weight change following 14 weeks insulin detemir treatment (± OADs); OADs, oral antidiabetic drugs

Figure 4  Weight change by baseline body mass index (BMI) category

Figure 5  Weight change vs. baseline body mass index (BMI)
long-acting insulin analogues has further minimised the risk of hypoglycaemia, especially nocturnal episodes (12,13,21). In addition, the analogue insulin detemir is associated with less weight gain compared with NPH insulin (13) and insulin glargine (16).

The OAD-treated, insulin-naïve, type 2 diabetes patients enrolled in the PREDICTIVE study had baseline blood glucose levels that were well above recommended targets, which was the main reason for initiating insulin detemir therapy. The majority of patients (82%) were receiving insulin detemir (± OADs) therapy with once daily injections at follow-up. Fourteen weeks of insulin detemir therapy (± OADs) improved glycaemic control, with a significant reduction in HbA1c, lower fasting glucose levels and lower within-patient fasting glucose variability. This was achieved in association with a low risk of hypoglycaemia. A modest decrease in body weight was also observed, which is in contrast to the weight gain that usually accompanies insulin initiation.

Weight gain is a key concern with insulin therapy in type 2 diabetes patients, particularly as overweight or obesity are common in this population (10). A weight gain of 2.5–7.5 kg is generally observed with insulin therapy during the first year (2,3). Clinical trials in patients with type 2 diabetes have reported less weight gain with insulin detemir vs. NPH insulin (12,22,23) and insulin glargine (16). In the present study, a body weight reduction was observed after 14 weeks of treatment with insulin detemir (± OADs), and this was most pronounced in obese patients (BMI ≥ 31 kg/m²).

Weight reduction after insulin initiation in diabetes patients with poor glycaemic control is an unusual finding. The reason for the observed weight reduction remains to be elucidated, but possible explanations include the non-controlled nature of the study, changes in diet, exercise and seasonal changes in weight. The reduction in weight may also relate to the discontinuation of insulin secretagogues and thiazolidinediones in some patients. However, a weight benefit (less weight gain) has been reported in clinical trials with insulin detemir (12,16).

Although observational studies are important in providing data about everyday clinical practice, they have inherent limitations. As mentioned above, concomitant medication and dietary intake were not controlled. More importantly, the study population does not have a control arm, is non-randomised, and a number of safety and efficacy parameters are based on patient recall, diaries or self-reported. It is, therefore, feasible that the findings could be attributed to a study effect. However, the cohort is diverse with regard to the number of countries, clinical centres and patients participating.

Conclusions

The 14-week follow-up data from OAD-treated, insulin-naïve, uncontrolled patients with type 2 diabetes from the European cohort of PREDICTIVE report that the initiation of insulin detemir (± OADs) was associated with improved glycaemic control (but still not optimal), a low incidence of total hypoglycaemia, no major hypoglycaemia and a small weight reduction. This was achieved in the majority of patients with once daily insulin administration. The results are consistent with clinical trial data (12,16). Longer-term follow-up from the PREDICTIVE study will provide additional data on the safety and efficacy of insulin detemir in clinical practice.

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