Transferring to insulin detemir from NPH insulin or insulin glargine in type 2 diabetes patients on basal-only therapy with oral antidiabetic drugs improves glycaemic control and reduces weight gain and risk of hypoglycaemia: 14-week follow-up data from PREDICTIVE™

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Aim: The aim of this study was to evaluate the safety and efficacy of insulin detemir in type 2 diabetes patients previously receiving NPH insulin (NPH group, n = 175) or insulin glargine (glargine group, n = 118) in combination with oral antidiabetic drugs (OADs).

Methods: Patients were transferred to insulin detemir, while the OAD regimen and number of injections remained the same. The incidence of serious adverse drug reactions, including major hypoglycaemia, and haemoglobin A1c (HbA1c), fasting glucose, within-patient fasting glucose variability and body weight change were measured at 14 weeks.

Results: Glycaemic control improved in both NPH (HbA1c = −0.2%, p < 0.05; fasting glucose −1.0 mmol/l, p < 0.0001) and glargine (HbA1c = −0.6%, p < 0.0001; fasting glucose −1.4 mmol/l, p < 0.0001) groups, including a reduction in fasting glucose variability (p < 0.01 for both). The incidence of total and nocturnal hypoglycaemia was reduced in both NPH and glargine groups. The incidence of major hypoglycaemia was low and did not change significantly during the follow-up period. Mean body weight was significantly reduced in the NPH (−0.7 kg, p < 0.01) and glargine (−0.5 kg, p < 0.05) groups.

Conclusions: These results indicate that in type 2 diabetes, transferring from other basal insulins to insulin detemir in combination with OADs was associated with improvements in glycaemic control, which were accompanied by a reduced risk of hypoglycaemia and a reduction in body weight.

Keywords: body weight, hypoglycaemia, insulin analogue, insulin detemir, type 2 diabetes

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Introduction

Disease progression in type 2 diabetes is directly related to the gradual failure of pancreatic beta-cell function [1]. Insulin therapy is, therefore, a key step in the management of type 2 diabetes and a natural progression in treatment. Despite the eventual necessity for insulin therapy [2], there is currently little guidance to aid physicians and patients in determining the optimal insulin type and administration regimen [3].

One simple regimen that is frequently adopted is the use of basal insulin in combination with oral antidiabetic drugs (OADs). Basal insulin suppresses excessive liver glucose production, which is the primary reason for the elevated fasting glucose concentrations in patients with type 2 diabetes [4], while insulin secretagogues are thought to provide prandial glucose regulation. In addition to efficacy, key considerations with respect to the use of any insulin regimen include the risk of hyperglycaemia (particularly nocturnal) and weight gain [5]. These undesirable side effects may have a significant impact on patient adherence to treatment [6–8]. Body weight, in particular, is a key concern for type 2 diabetic patients, many of whom are overweight or obese at diagnosis.

The development of long-acting basal insulin analogues with improved pharmacokinetics, which are able to more closely replicate endogenous insulin secretion, has been shown to have a positive effect on the balance between effective glycaemic control and hypoglycaemic risk [9–14]. In the randomized controlled clinical trials involving patients with type 2 diabetes, the long-acting analogue insulin detemir (either as a component of basal–bolus therapy or added to existing OAD therapy) was associated with improved glycaemic control and significantly less within-patient fasting blood glucose variability, when compared with NPH insulin [9–11]. This improvement in glycaemic control was accompanied by significant reductions in overall and nocturnal hypoglycaemia [11]. Another benefit found in clinical trials with insulin detemir was less weight gain compared with NPH insulin [9–11] and insulin glargine-based regimens [15].

While these clinical trial findings are promising, they are based on defined patient populations under controlled conditions and are not able to demonstrate the efficacy and safety of insulin detemir in everyday clinical practice. The primary objective of PREDICTIVE™ (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation) – a multinational, multicentre, open-label observational study – is to evaluate the safety and efficacy of insulin detemir in a diverse patient population as part of their routine care. Fourteen-week follow-up data from the European cohort of the PREDICTIVE study have been reported previously [16].

Here, we report an analysis of patients with type 2 diabetes who were previously receiving basal insulin – NPH insulin (NPH group) or insulin glargine (glargine group) – in combination with OADs. We assess whether transferring to the analogue insulin detemir, while maintaining the same number of injections and OAD regimen, conferred any clinical benefits in terms of safety and/or efficacy, in particular, in incidence of hypoglycaemia and body weight change.

Materials and Methods

Study Design

PREDICTIVE is a multinational, open-label, prospective, uncontrolled observational study. The study aims to evaluate the safety and efficacy of insulin detemir over 12, 26 or 52 weeks (in specific countries) in patients (male and female) with type 1 or type 2 diabetes. In addition, this study aims to confirm findings from previous clinical trials but in an uncontrolled environment as reflected in routine practice. Here, we report 14-week patient data from 11 countries in the European cohort (Austria, Czech Republic, Denmark, Finland, Germany, Ireland, Israel, the Netherlands, Sweden, Turkey and the UK). The study was performed in accordance with the regulatory requirements for observational studies in each country.

Patient Population

The European cohort of PREDICTIVE comprised a total of 20,531 patients, of whom 12,981 had type 2 diabetes. Of these patients, 3,986 were receiving treatment with insulin and OADs at baseline (figure 1). Two hundred and ninety-three of these patients who had been receiving treatment with OADs and one or two basal injections of NPH insulin or insulin glargine at baseline were transferred to insulin detemir while retaining the same number of daily insulin injections and the same OAD regimen (OAD type remained the same).

This subpopulation of the PREDICTIVE study was evaluated to assess the impact of transferring from a conventional insulin (NPH insulin) to an insulin analogue (insulin detemir) and furthermore to assess whether there was any impact of transferring between two different insulin analogue types (insulin glargine vs. insulin detemir) in patients with type 2 diabetes.
Baseline demographics, including physicians’ reasons for initiating insulin detemir, are presented in table 1. The demographics of the patients selected for this analysis were similar to those of the total type 2 diabetes cohort. The main reasons for transferring to insulin detemir in both groups were to improve glycaemic control and to reduce fasting glucose variability. The proportion of patients with haemoglobin A1c (HbA1c) levels <7.0% at baseline was 12.7% (n = 165) and 13.2% (n = 106) for the NPH and glargine groups respectively. The only criterion for PREDICTIVE study enrolment was a decision by the patient’s physician to initiate insulin detemir therapy as part of routine clinical care. Exclusion criteria were limited to the following: low likelihood of cooperation, previous treatment with insulin detemir, previous enrolment in PREDICTIVE and hypersensitivity to insulin detemir or any of its excipients.

**Treatment Regimen**

Patients requiring basal insulin were prescribed insulin detemir by their treating physician as part of routine clinical care. The starting dose and subsequent adjustments to the treatment regimen were at the individual physician’s discretion. Inclusion and exclusion criteria have been reported previously [17].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NPH group (n = 175)</th>
<th>Glargine group (n = 118)</th>
<th>Total type 2 diabetes cohort (n = 12,981)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (% patients)</td>
<td>48.6/51.4</td>
<td>48.3/51.7</td>
<td>47.0/53.0</td>
</tr>
<tr>
<td>Mean age (years) ± s.d.</td>
<td>60.9 ± 10.9</td>
<td>63.5 ± 11.4</td>
<td>60.6 ± 10.8</td>
</tr>
<tr>
<td>Mean diabetes duration (years) ± s.d.</td>
<td>11.6 ± 7.0</td>
<td>9.9 ± 6.5</td>
<td>11.2 ± 7.5</td>
</tr>
<tr>
<td>Mean BMI (kg/m²) ± s.d.</td>
<td>31.5 ± 6.1</td>
<td>30.1 ± 4.9</td>
<td>30.9 ± 5.9</td>
</tr>
<tr>
<td>Physician reason for initiating detemir (%)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improve glycaemic control</td>
<td>79</td>
<td>84</td>
<td>87</td>
</tr>
<tr>
<td>Reduce risk of hypoglycaemia</td>
<td>32</td>
<td>18</td>
<td>20</td>
</tr>
<tr>
<td>Try new insulin</td>
<td>20</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Improve weight control</td>
<td>35</td>
<td>43</td>
<td>35</td>
</tr>
<tr>
<td>Reduce plasma glucose variability</td>
<td>47</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Change because of insulin pen</td>
<td>4</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Patient dissatisfaction with current therapy</td>
<td>20</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>Unstable diabetes</td>
<td>7</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Side-effects of current therapy</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>1</td>
<td>9</td>
<td>4</td>
</tr>
</tbody>
</table>

BMI, body mass index.

*More than one reason may have been stated.
In the subgroup reported in this article, patients previously receiving once- or twice-daily NPH insulin or insulin glargine in combination with OADs were transferred to the same number of insulin detemir injections without change in their OAD regimen (figure 1). Follow-up visits were scheduled at 12 weeks. However, because of the uncontrolled nature of the study, results were obtained after a mean follow-up period of 14.4 weeks. It was the responsibility of the individual physician to ensure that patient follow-up schedule was followed as accurately as possible.

Primary and Secondary Endpoints

The primary endpoint of the overall study was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic episodes. Secondary endpoints included the incidence of total and nocturnal hypoglycaemic episodes, HbA1c, mean self-monitored fasting glucose (fasting blood glucose or fasting plasma glucose depending on the glucose meter used), within-patient fasting glucose variability (calculated as the standard deviation of the last two to six fasting glucose measurements). Number of measurements for analysis was based on measurements provided by the patient at baseline and at 12-week follow-up and change in body weight.

Safety and efficacy parameters were collected from patient records, recall and patient diaries. Measurements of all study parameters (either at the clinic or self-reported) depended on routine practice. This was believed to be consistent for each patient at the baseline as well as at the follow-up visit and to not distort results. SADRs were recorded for the entire observation period. The incidence of hypoglycaemic episodes was measured at 4 weeks prior to transferring to insulin detemir and again in the 4 weeks before follow-up. Body weight was measured at the clinic or self-reported by patients. All these data were collected and verified by the patient’s physician. These data from each country were then gathered together on a central database for the purposes of analysis. Further details on safety and efficacy parameters for the main study population have been reported previously [16].

Statistical Analysis

Data were pooled from all patients previously receiving NPH insulin or insulin glargine with OADs, who were transferred to insulin detemir with the same OAD regimen (figure 1). Efficacy analyses included data from all subjects who received at least one dose of insulin detemir and had at least one efficacy measurement at baseline and during 8–18 weeks of commencing insulin detemir. Safety analyses included data from all subjects who received at least one dose of insulin detemir.

Demographic characteristics, HbA1c, fasting glucose, weight, body mass index values and hypoglycaemic episodes are summarized with descriptive statistics, including mean and standard deviation 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 Wilcoxon paired sign rank sum test for discrete variables such as incidence of hypoglycaemic episodes. A p value of less than 0.05 was considered statistically significant.

Results

SADRs and Hypoglycaemia

A detailed description of the SADRs for the total number of patients included in the 11 countries has been reported previously [16]. There were no SADRs reported for the subgroup of type 2 patients presented here. In the 4 weeks prior to follow-up, one major hypoglycaemic episode was reported (not as SADR) by a patient receiving NPH insulin.

In the NPH group, transfer to insulin detemir was associated with a significant decrease in the incidence of total hypoglycaemia from 11.7 to 3.0 episodes/patient-year (0.9–0.2 episodes per 4 week period, p < 0.0001; figure 2). The incidence of nocturnal hypoglycaemia was also reduced by 5.5 episodes/patient-year (0.4 episodes per 4 week period, p < 0.0001). There were 0.07 major hypoglycaemic episodes/patient-year (0.01 episodes per 4 week period) reported in the last 4 weeks prior to follow-up visit compared with 0.78 episodes/patient-year (0.06 episodes per 4 week period) in the 4 weeks prior to study start.

In the glargine group, following insulin detemir therapy, the incidence of total hypoglycaemia was significantly reduced from 4.3 to 0.8 episodes/patient-year (0.33–0.1 episodes per 4 week period, p < 0.01; figure 2). Nocturnal hypoglycaemia was reduced by 1.2 episodes/patient-year (0.1 episodes per 4 week period, p < 0.05). There were no major hypoglycaemic episodes reported in the last 4 weeks prior to follow-up visit compared with 0.26 episodes/patient-year (0.02 episodes per 4 week period) prior to study start.

Glycaemic Control and Insulin Dose

Significant improvements in glycaemic control were observed following treatment with insulin detemir in
both the NPH and glargine groups. In the NPH group, mean HbA1c was reduced by 0.2% (p < 0.05; table 2). There were also reductions in fasting glucose [1.0 mmol/l (18.0 mg/dl), p < 0.0001] and fasting glucose variability [0.4 mmol/l (7.2 mg/dl), p < 0.001].

In the glargine group, mean HbA1c was reduced by 0.6% (p < 0.0001). Reductions were also observed in fasting glucose [1.4 mmol/l (25.2 mg/dl), p < 0.0001] and fasting glucose variability [0.3 mmol/l (5.4 mg/dl), p < 0.01].

At follow-up, the majority of patients received insulin detemir once daily (74.3 and 93.2% in the NPH and glargine groups respectively). Both at baseline (based on pre-study regimes) and at follow-up, the majority of patients received insulin determin once-daily (74.3% and 93.2% in the NPH and glargine groups, respectively). The mean basal insulin dose at follow-up increased in both the NPH and glargine groups (0.07 IU/kg and 0.05 IU/kg respectively). The mean basal insulin dose at follow-up increased in both the NPH and glargine groups (0.07 and 0.05 IU/kg respectively).

**Body Weight**

Mean body weight following insulin detemir therapy was reduced by 0.7 kg in the NPH group (p < 0.01) and by 0.5 kg in the glargine group (p < 0.05; figure 3).

**Discussion**

In the subgroup of patients reported here, glycaemic control at baseline was suboptimal, regardless of the basal

### Table 2 Change in glycaemic control after 14 weeks of insulin detemir therapy

<table>
<thead>
<tr>
<th></th>
<th>NPH group</th>
<th>Glargine group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c (%) ± s.d.</td>
<td>(n = 152)</td>
<td>(n = 97)</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.1 ± 1.4</td>
<td>8.1 ± 1.2</td>
</tr>
<tr>
<td>Follow-up</td>
<td>7.9 ± 1.6</td>
<td>7.5 ± 1.2</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−0.2 ± 1.2</td>
<td>−0.6 ± 0.9†</td>
</tr>
<tr>
<td>Mean self-monitored fasting glucose (mmol/l) ± s.d.</td>
<td>(n = 121)</td>
<td>(n = 88)</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.5 ± 2.2</td>
<td>9.0 ± 2.5</td>
</tr>
<tr>
<td>Follow-up</td>
<td>7.5 ± 2.1</td>
<td>7.6 ± 1.9</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−1.0 ± 2.2</td>
<td>−1.4 ± 2.4‡</td>
</tr>
<tr>
<td>Mean within-patient fasting glucose variability (mmol/l) ± s.d.</td>
<td>(n = 105)</td>
<td>(n = 69)</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.3 ± 1.2</td>
<td>1.2 ± 1.0</td>
</tr>
<tr>
<td>Follow-up</td>
<td>1.0 ± 0.8</td>
<td>0.9 ± 0.7</td>
</tr>
<tr>
<td>Mean change from baseline</td>
<td>−0.4 ± 1.1</td>
<td>−0.3 ± 1.0**</td>
</tr>
</tbody>
</table>

HbA1c, haemoglobin A1c. *p < 0.05 vs. baseline; **p < 0.01 vs. baseline; †p < 0.001 vs. baseline; ‡p < 0.001 vs. baseline.
insulin utilized, and this was the most common reason for transferring to insulin detemir. In addition, despite baseline HbA1c being above current guideline targets, hypoglycaemia was occurring with moderate frequency, especially in patients who were previously receiving NPH insulin. This was also a key reason for initiating insulin detemir. In both the NPH and glargine groups, patients were obese at baseline and weight control was therefore another reason for transferring to insulin detemir in a substantial proportion of the study population.

These 14-week follow-up data from 11 countries in the European cohort of the PREDICTIVE study suggest that in type 2 diabetic patients treated with basal insulin in combination with OADs, transfer to insulin detemir from NPH insulin or insulin glargine resulted in improved and more predictable glycaemic control, with a reduction in mean HbA1c of up to 0.6%. This was achieved with small increases in insulin dose.

The HbA1c data obtained in this study were associated with considerable variability. This variability comprises intra-assay, interassay and interpatient variability. Intra-assay variability has been well documented [18], and as clinicians participating in the PREDICTIVE study measured HbA1c levels using the standard assay procedure of their clinic, the extent to which assays were standardized (e.g. using Diabetes Control and Complications Trial-aligned or International Federation of Clinical Chemistry reference method techniques) is not known. It should be noted, however, that all HbA1c evaluations from an individual patient were performed in the same laboratory. The overall magnitude of the variability in HbA1c in the PREDICTIVE study is similar to that described in other, much larger studies such as the United Kingdom Prospective Diabetes Study, in which assays were performed at a central laboratory [5]. Moreover, in spite of the variability in the HbA1c data in the current study and the relatively small patient numbers, the reductions in HbA1c that occurred during the 3-month study were statistically significant in both patient groups.

The improvements in glycaemic control observed in this study were accompanied by significant reductions in the risk of total and nocturnal hypoglycaemia in patients previously receiving NPH insulin and insulin glargine. A statistically significant weight loss was observed in patients transferred from NPH insulin and insulin glargine to insulin detemir. The reduction in hypoglycaemia and the weight reduction observed with insulin detemir in the present study suggest that more aggressive titration of insulin doses with a lower incidence of side-effects may be feasible in patients with type 2 diabetes.

The PREDICTIVE study was designed to assess the safety and efficacy of insulin detemir outside the limitations of the strictly controlled setting of a randomized controlled trial, thus providing valuable information for the ‘real-world’ setting. It should be noted that the non-randomized non-controlled nature of the study has clear limitations. For example, a study effect cannot be ruled out, and this may have influenced the observed improvements in HbA1c and hypoglycaemia. However, analysis of 12-month data in the future should not be subject to the same level of potential study effects. This form of study also has its advantages. The overall patient population in the PREDICTIVE study is very large and is generally a representative of the range of insulin-treated diabetes patients seen by primary and secondary care physicians, and the study is performed within real-life medical practices. The patients, in effect, act as their own controls, before and after insulin detemir initiation. This study design strengthens the clinical relevance of the results for routine clinical care of patients with type 2 diabetes.

It is relevant to note that the reductions in weight gain and incidence of hypoglycaemia noted in the current study support the results of randomized controlled clinical trials that have evaluated insulin detemir in a basal–OAD regimen. In a study involving insulin-naïve patients where NPH insulin was the comparator, the addition of insulin detemir to OADs was associated with significantly less weight gain and a reduction in overall and nocturnal hypoglycaemia [11]. When compared with insulin glargine in insulin-naïve patients, insulin detemir was associated with significantly less weight gain and a comparable risk of hypoglycaemia [15]. These results, particularly those showing a weight-sparing
effect, were surprising, and it was therefore important to demonstrate that they were achievable in the ‘real world’, outside the controlled conditions of a randomized controlled trial. Our present results, which are derived from a cohort that is diverse with regard to the number of countries, clinical centres and patients participating in the study, suggest that these benefits of insulin detemir may be translated into clinical practice.

Longer term results from the PREDICTIVE study will provide further information on the safety and efficacy of insulin detemir when used in different insulin regimens for the management of diabetes in clinical practice and supply details of diabetes treatment and glycaemic control across the world.

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References