From insulin detemir to glargine: Effect on glycemic control and psychological wellbeing in patients with diabetes mellitus type 2 in daily practice#

Thiemo F. Veneman1*, Fred E. M. G. Storms2, Ingo A. Eland3, Paul K. P. Bouter4

1Department of Internal Medicine, Ziekenhuisgroep Twente, Almelo, Netherlands; *Corresponding Author: tfveneman@hetnet.nl
2Department of Internal Medicine, Sint Antoniusziekenhuis, Utrecht, Netherlands
3Department of Internal Medicine, Sint Antoniusziekenhuis, Nieuwegein, Netherlands
4Department of Internal Medicine, Jeroen Bosch Ziekenhuis, ’s-Hertogenbosch, Netherlands

Received 29 November 2011; revised 31 December 2011; accepted 17 January 2012

ABSTRACT
The success of a specific treatment is traditionally judged according to parameters such as HbA1c. However, other, patient-reported outcomes (PRO) of (insulin) therapy, become increasingly more important. The introduction of (basal) insulin-analogues could possibly improve PRO, particularly “quality of life”. Direct comparative studies between once daily insulin glargine and once to twice or twice daily insulin detemir have previously shown differences in insulin dosage, dosing frequency and weight gain. Whether this leads to a difference in quality of life in patients who are transferred from insulin detemir to insulin glargine remains to be determined. To establish the effect of insulin glargine on quality of life and patient satisfaction in patients with DM2 who are in poor metabolic control with a (human) basal insulin, a large prospective, observational study in Dutch daily practice was performed. The results of the patient population switched from NPH-insulin to insulin glargine have been published previously. In this article the results of the group of patients treated with insulin detemir before the observation period are described. The results of this observational study show that changing basal insulin therapy to insulin glargine in patients with DM2 who are in poor glycemic control with insulin detemir leads to a clinically significant improvement of glycemic control as well as emotional wellbeing, despite a small increase in weight. Whether other factors such as decreased dosing frequency play a role remains to be determined by future studies.

Keywords: Insulin Glargine; Insulin Detemir; Psychological Wellbeing; Metabolic Control; Type 2 Diabetes

1. INTRODUCTION
Diabetes mellitus type 2 (DM2) is characterized by insulin resistance and a progressive decline of the insulin secretory capacity. This pathophysiological mechanism necessitates intensification of therapy in time for most patients [1]. As a consequence the majority of patients with DM2 become dependent on treatment with insulin, with or without the combination with oral glucose lowering medication [2]. It is important to realize that good glycemic control, early in the disease process, is needed to prevent long-term (cardio)vascular complications [3]. Different guidelines, such as the ADA/EASD consensus statement and the Dutch (NHG) standard Diabetes Mellitus type 2, are focused on timely intensification of treatment [4,5]. If good glycemic control cannot be reached by oral glucose-lowering medication alone, addition of once daily basal insulin is considered to be the next step. However, several studies show that in many instances this does not occur in daily practice [6,7]. One retrospective cohort analysis based on the THIN (The Health Improvement Network) database showed that 50% of patients with DM2 who were in insufficient metabolic control on oral glucose lowering medication alone received treatment with insulin not until 4.9 years later [6]. The postponement of insulin therapy is based on negative perceptions regarding insulin in patients as well as in doctors. Among them are supposed complexity of the treatment, worries about wellbeing, fear for weight increase and fear for hypoglycemia [8-14]. It is not fully clear to what extent insulin therapy influences the quality of life and/or patient satisfaction regarding therapy. Apart from studies showing a beneficial effect on these pa-
rameters [15-18], there are even so studies showing a neutral [19,20] or a negative effect [21-23].

Apart from the traditional parameters such as HbA1c, other, patient reported outcomes (PRO) of (insulin) therapy, become an increasingly more important part in the judgment of the success of a specific treatment [24]. The introduction of (basal) insulin-analogues could possibly improve PRO, particularly with regards to quality of life [17,18]. Direct comparative studies between once daily insulin glargine and once to twice or twice daily insulin detemir have previously shown no clinically relevant difference in glycemic control and equal low number of hypoglycemic events. However differences in insulin dosage, dosing frequency and weight gain were observed. Whether this leads to a difference in quality of life in patients who are transferred from insulin detemir to insulin glargine remains to be determined. To establish the effect of insulin glargine on quality of life and patient satisfaction in patients with DM2 who are in poor metabolic control with a (human) basal insulin, a large prospective, observational study in Dutch daily practice was performed [25]. The results of the patient population switched from NPH-insulin to insulin glargine have been published previously [25]. In this article the results of the group of patients treated with insulin detemir before the observation period are described.

2. METHODS

2.1. Patient Selection

The observational ESPRIT (Effect Study on Patient Reported outcomes in Insulin glargine Treatment) study was performed between 2005 and 2008 [25]. In 116 centers in The Netherlands patients with DM2 on NPH-insulin, mixed insulin or insulin detemir ± oral glucose lowering medication ± short acting-insulin were asked to participate in the study by their doctor, after the decision was made that the current basal insulin needed to be replaced by once daily insulin glargine. The decision to start with insulin glargine was taken by the caregiver based on clinical decisionmaking and thus independent of participation in the study. Participation in the study did not interfere with normal daily practice. Patients were asked to fill out a questionnaire on three different occasions which took approximately 15 minutes. Because the study had an observational and non-invasive character approval of an ethical committee was not needed. A total number of 510 patients participated in the study, 83 of them initially treated with insulin detemir. Clinical parameters as well as PRO were measured at baseline and at 3 and 6 months respectively.

2.2. Measurements

Demographic and clinical data were obtained by self-reporting and consisted of age, gender, body weight, time since diagnosis, use of medication, frequency of hypoglycemia, presence of diabetes related complications as well as co-morbidity. At baseline as well as during the follow-up visits after 3 and 6 months HbA1c and fasting glucose concentration were measured. Adverse events were recorded and treated accordingly by the physician.

PRO for the establishment of patient well being consisted of three validated questionnaires. The Dutch version of the “Worry subscale” of the “Hypoglycaemia Fear Survey” (HFS-w), a validated 13-item questionnaire, was used to measure worrying about hypoglycemia [26]. To clarify interpretation of the data the HFS-w scores were transformed to a “0-to-100-scale”. The commonly used “Diabetes Symptom Checklist-revised” (DSC-r) was used to measure the severity of diabetes related symptoms. The DSC-r consists of 34 items, grouped in 8 subscales: hyperglycemia, hypoglycemia, cognitive defects, fatigue, cardiovascular problems, neuropatic pain, neuropathic sensitivity and ophthalmologic functioning [27,28]. Each item of the DSC-r asks for the presence or absence of specific symptoms (yes/no) and, if present, to which extent on a 5-point Likert scale. Next the scores are transformed to a 0 tot 100 score in order to obtain the DSC-r total score. A similar transformation is applied on different DSC-r subscales. General emotional wellbeing was measured with the WHO-5 wellbeing index [29]. The WHO-5 measures positive mood, vitality and general interest. Item scores are added in order to obtain a total wellbeing-score and transformed to a 0 to 100 scale. Low scores indicate less wellbeing. The WHO-5 questionnaire is a suitable method to screen for depressive mood disorders with a cutoff score of 28 [30].

2.3. Statistical Analysis

The primary variable was change of the PRO’s: HFS-w, DSC-r, and WHO-5 from baseline (before initiation of treatment with insulin glargine) to 3 and 6 months after initiation of treatment with insulin glargine. This was determined with “time” as an independent dummy variable using the Generalized Estimating Equations (GEE) analysis. Secondary variables (change in HbA1c, fasting blood glucose, the number of symptomatic, nocturnal and severe hypoglycemic episodes during the past month and bodyweight after 3 and 6 months) were analyzed in a similar fashion. If variables were not normally distributed they were transformed according to a natural logarithm. This was the case for the number of symptomatic, nocturnal and severe hypoglycemic episodes during the past month, the HFS-w, DSC-r total score and the subscales of the DSC-r. Because of the setting of the study which is performed in daily practice and the lack of controls, observational studies in general are at risk to miss

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In order to optimize the use of available data several imputation techniques are available. In this study we choose for the technique of multiple imputation, presently the most robust method to handle missing data [31]. Analyses are performed using STATA, version 10.0 (StataCorp, College Station, TX, USA). P-values < 0.05 were considered to be statistically significant.

3. RESULTS

Baseline demographic data and change in time of clinical parameters are shown in Table 1. Prior to the start of treatment with insulin glargine out of the 510 patients with DM2 from the total ESPRIT cohort 280 patients were treated with NPH-insulin, 147 with mix-insulin and 83 with insulin detemir. In the patients treated with insulin detemir the mean dose of the basal insulin at baseline was 39 ± 26 units per day, comparable to the mean dose of insulin glargine at the start of the study (39 ± 22 units per day). In addition to the basal insulin, patients in the insulin detemir group used other glucose lowering medication: oral medication (N = 7, 8%), other insulin (N = 56, 67%) or a combination of both (N = 20, 24%).

The mean HbA1c at baseline was 8.4% ± 1.1% and decreased to 8.0 ± 1.2% after 3 months. The decrease was persistent, with an HbA1c of 8.0% ± 3.1% at the end of the observation period of 6 months (p = 0.001 vs. baseline, Table 1). Comparable data were found regarding the decrease of the fasting blood glucose concentration (FBG). The FBG decreased from 10.3 ± 3.8 mmol/L at baseline to 8.7 ± 3.0 mmol/L after 3 months and 8.6 ± 3.1 mmol/L after 6 months of follow-up (p = 0.001 vs. baseline). The improvement of glycemic control was accompanied by a slight increase of the BMI as well as of the use of the total units of basal insulin (Table 1).

At baseline 66% of the patients indicated to have had a symptomatic hypoglycemic episode in the 3 months prior to the start of the study. This number does not change significantly during follow-up, 70% after 6 months (p = 0.475). At baseline the percentage of patients with 1 or more nocturnal hypoglycemic episodes in the 3 months prior to the start of the study was 37% at baseline. The number of patients indicating to have an episode of nocturnal hypoglycemia remained unchanged after 3 months (29%) but significantly decreased to 22% after 6 months (p < 0.044). The number of patients indicating to have an episode of severe hypoglycemia, 8%, (N = 7) did not change during the follow-up period.

The results regarding the changes of PRO are shown in Figure 1 and in Table 2. The DSC-r score decreases significantly from 17 ± 14 at baseline to 15 ± 13 after 3 months of follow-up (p = 0.016). This decrease is continued during the second observation period to 12 ± 12 after 6 months (p < 0.001 vs. baseline). The data on the DSC-r subscales are shown in Table 2. At baseline the subscale “fatigue” is particularly being indicated to be a diabetes related symptom that negatively influences wellbeing. This subscale significantly improves after 3 months and remains improved until the end of the observation period (Table 2).

The baseline score for the WHO-5 was 51 ± 24 and

<table>
<thead>
<tr>
<th>Table 1. Baseline population characteristics and changes in clinical parameters.</th>
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<tbody>
<tr>
<td>Baseline</td>
</tr>
<tr>
<td>N</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Gender (% ♀)</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
</tr>
<tr>
<td>Education (% low level education)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Glycemic parameters</td>
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<tr>
<td>HbA1c (%)</td>
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<tr>
<td>FBG (mmol/L)</td>
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<tr>
<td>Insulin dose</td>
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<tr>
<td>Insulin detemir (IU/day)</td>
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<td>Insulin glargine (IU/day)</td>
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</table>
Figure 1. Change in PRO van from baseline to 6 months follow-up. (a): Diabetes Symptom Checklist-revised (DSC-r, scale 0 - 100, lower score indicates less complaints, (b): WHO-5 wellbeing score (WHO-5, scale 0 - 100, higher score indicates better wellbeing), (c): Hypoglycemia Fear Survey (HFS-w, scale 0 - 100, higher score indicates less fear for hypoglycemia). P-value represents significance compared to baseline value.
improved to 60 ± 22 after 3 months and to 65 ± 23 after 6 months (p < 0.001 vs. baseline). Even after correction for glycemic control, by means of HbA1c similar WHO-5 scores are found (data not shown). At the beginning of the observation period approximately half of the patients (51%, N = 42) has a suboptimal or even lower WHO-5 score. This percentage significantly improved to 22% (N = 18) after 6 weeks of treatment with insulin glargine. The HFS-w scores (worries about hypoglycemia) were low at baseline and remained unchanged during the remainder of the study.

### 4. DISCUSSION

The results of this 6-month, observational study show that conversion of the treatment from insulin detemir to insulin glargine in patients with DM2 as their basal insulin analogue induces a significant improvement in glycemic control and emotional wellbeing in Dutch daily practice.

International treatment guidelines, such as the ADA/EASD consensus statement, suggest that the use of insulin-analogues with a longer duration of action and a peak-less pharmacologic profile, leads to a diminished prevalence of (nocturnal) hypoglycemia compared to NPH-insulin [5]. A large number of studies confirm these findings [32-35]. Recently several head-to-head randomised clinical trials have compared both basal insulin-analogues, both in insulin-naïve patients and in patients using a basal-bolus insulin regimen [36-39]. In addition to the separate study results a recent Cochrane review shows an equal low number of hypoglycemic events and no clinically relevant difference in glycemic control between once daily insulin glargine and once to twice daily insulin detemir [36-39]. There are, however, differences with respect to other, clinically relevant, secondary endpoints such as insulin dosage and dosing frequency and weight gain. In patients with DM2 using either basal insulin analogue in addition to oral medication up to 75% higher doses of insulin detemir are needed compared to insulin glargine to reach similar levels of glycemic control [36,37,40,41]. In addition, dosing frequency of insulin glargine appeared to be lower compared to insulin detemir, whereas weight gain was lower for insulin detemir [36-40]. Although it can be argued that a lower dosing frequency has a positive influence on treatment satisfaction and (hence) treatment adherence [42], the same can be argued for lower weight gain. Data from the L2T3 study suggest that treatment with once daily insulin glargine result in better patient satisfaction compared to treatment with twice daily insulin detemir, despite a difference of 0.8 kg in weight gain [37].

In the present study both the DSC-r score as well as the emotional wellbeing (WHO-5) show significant improvements, despite a small increase in BMI during the 6 months observation period. A similar observational study in the Netherlands in insulin-naïve patients starting insulin glargine treatment also showed that modest weight gain following insulin glargine initiation in DM2 was not associated with deterioration of HRQoL [43].

The average improvement of the WHO-5 score was 14 points, which is more than, according to the authors of the WHO-5 questionnaire, is considered to be clinically relevant [44]. Based on the DSC-r subscales it can be concluded that especially the scales associated with “fatigue” and “hyperglycemia” comprise the problems associated with a decrease in wellbeing. Indeed these are also the scales that show a significant improvement, in contrast to the robust subscale “neuropathic pain”. Fear for hypoglycemia does not diminish after 6 months which is in accordance with the finding that the number of hypoglycemia events decreased.

### Table 2. Change in DSC-r subscales over time.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>p-value (baseline – 6 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSC-r Total</strong></td>
<td>17 ± 14</td>
<td>15 ± 13</td>
<td>12 ± 12</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>DSC-r subscales</strong></td>
<td></td>
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<tr>
<td>Hyperglycemia</td>
<td>21.5 ± 22.0</td>
<td>15.4 ± 18.2</td>
<td>11.4 ± 14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>16.8 ± 19.4</td>
<td>14.1 ± 15.5</td>
<td>9.3 ± 13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cognition</td>
<td>18.0 ± 20.1</td>
<td>14.4 ± 17.4</td>
<td>11.8 ± 14.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>33.9 ± 27.0</td>
<td>26.3 ± 25.9</td>
<td>22.8 ± 24.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>13.3 ± 16.0</td>
<td>11.2 ± 14.8</td>
<td>8.6 ± 11.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>14.2 ± 19.4</td>
<td>13.0 ± 18.4</td>
<td>12.3 ± 16.6</td>
<td>0.312</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>12.1 ± 19.3</td>
<td>14.4 ± 19.4</td>
<td>14.3 ± 30.3</td>
<td>0.314</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>11.9 ± 16.9</td>
<td>9.2 ± 16.2</td>
<td>8.5 ± 14.9</td>
<td>0.023</td>
</tr>
</tbody>
</table>
glycemic episodes does not change after 6 months.

An advantage of the observational character of the current study is that the results obtained in a strict controlled setting and in a selected patient population such as in a randomised controlled trial, are derived from daily real-life clinical practice. Simultaneously this advantage implies a disadvantage: the observational setting can cause selection bias. However, several arguments suggest that there was no such bias in this study. First, baseline HbA1c was 8.4% suggesting that there was a good medical indication for the included patient population to change basal insulin therapy. Second, socio-economic patient characteristics show that the study population is representative for a patient population in normal clinical practice. Third, the improvements regarding the HbA1c represent a patient population in normal clinical practice. Simultaneously this advantage implies a disadvantage: the observational setting can cause selection bias. However, several arguments suggest that there was no such bias in this study. First, baseline HbA1c was 8.4% suggesting that there was a good medical indication for the included patient population to change basal insulin therapy. Second, socio-economic patient characteristics show that the study population is representative for a patient population in normal clinical practice. Third, the improvements regarding the HbA1c and WHO-5 score, wellbeing appeared to improve significantly.

In conclusion the results of this observational study show that changing basal insulin therapy to insulin glargine and subsequent improvement in glycemic control. This is corroborated by the fact that only during the first 3 months a small increase in insulin dose was found with a concomitant improvement in HbA1c percentage, whereas the wellbeing continued to improve after these first 3 months, represented by a significant improvement of the WHO-5 and DCS-r scores from months 3 to 6. Finally, even after correction for HbA1c of the WHO-5 score, wellbeing appeared to improve significantly.

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5. ACKNOWLEDGEMENTS

The results of this study are based on a sub study of the ESPRIT project, funded by sanofi-aventis Netherlands [25]. Data-analysis was performed by T. Hajos, MSc at the Free University Medical Centre. Financial support was given by sanofi-aventis Netherlands.

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