

Insulin glargine benefits patients with type 2 diabetes inadequately controlled on oral antidiabetic treatment: an observational study of everyday practice in 12,216 patients

S. A. Schreiber¹ and T. Haak²

¹Diabetologe DDG, Quickborn, Germany

²Diabetes-Zentrum Mergentheim, Bad Mergentheim, Germany

Aims: This observational study aimed to investigate the long-term efficacy and safety of adding insulin glargine (LANTUS®) to support oral antidiabetic (OAD) treatment in patients with type 2 diabetes in everyday practice.

Methods: A 9-month, open-label, multicentre, observational study, with an optional 20-month extension phase, in which add-on insulin glargine therapy was initiated in 12,216 patients with type 2 diabetes inadequately controlled on OADs. The insulin glargine dose was adjusted at the physician's discretion, reflecting everyday practice. The main outcome measures were changes in HbA_{1c}, fasting blood glucose (FBG), insulin dose and body mass index (BMI).

Results: At baseline, mean (\pm s.d.) age was 63.9 ± 11.3 years; disease duration was >5 years in 47% of patients, 1–5 years in 39% of patients and <1 year in 10% of patients, while 4% of patients were newly diagnosed. Addition of insulin glargine to OAD therapy led to reductions in mean HbA_{1c} (-1.5% from 8.7%) and FBG (-69 mg/dl from 202 mg/dl) levels after 3 months, which were maintained after 9 months [HbA_{1c}: -1.7% ; FBG: -71 mg/dl (-3.9 mmol/l)] without an increase in BMI. Similar glycaemic control was observed after 20 months in the 2721 patients in the extension study. Adverse drug reactions were documented in 26 patients (0.2%). Of 47 adverse events documented, 19 were due to hypoglycaemia.

Conclusions: In everyday practice, patients with type 2 diabetes who are inadequately controlled on OADs benefit from add-on basal insulin treatment with insulin glargine as they demonstrate improved glycaemic control without weight gain.

Keywords: insulin glargine, observational study, type 2 diabetes

Received 22 November 2005; accepted 20 January 2006

Introduction

The prevalence of diabetes is increasing worldwide and is projected to double between 2000 and 2030 to an estimated 4.4% of all age groups [1]. The prevalence of diabetes in Germany is currently estimated at 7% of the population and is increasing [2].

Type 2 diabetes is characterized by defects in insulin secretion and increased insulin resistance. While type 2

diabetes may initially be controlled through diet and exercise, eventually the introduction of oral antidiabetic agents (OADs) is required to maintain glycaemic control [3]. As the disease progresses, management becomes increasingly difficult with OADs alone, necessitating the addition of insulin therapy [4]. Initiating insulin treatment at an early stage of type 2 diabetes to support OAD therapy has been shown to significantly improve

Correspondence:

S. A. Schreiber, MD, Diabetologe DDG, Schillerstrasse 28, Quickborn 25451, Germany.

E-mail:

stephan.schreiber@diabetes-hamburg.de

glycaemic control (HbA_{1c} and blood glucose) and thereby reduce the risk of late complications associated with the disease [5]. It has also been shown that when insulin therapy with insulin glargine (LANTUS®) is initiated in early type 2 diabetes, patients failing on OADs benefit from lower rates of hypoglycaemia and less weight gain compared with patients initiated on insulin therapy at later stages of the disease [6].

The intermediate-acting insulin NPH insulin has traditionally been used for insulin introduction in patients with type 2 diabetes. However, NPH insulin often requires twice-daily injections to provide 24-h insulin coverage and demonstrates a peak of activity 4–6 h after administration. This often leads to a sharp fall in blood glucose levels and increases the risk of hypoglycaemia, particularly nocturnal hypoglycaemia following bedtime administration [7–10].

Insulin glargine is a long-acting insulin analogue that more closely mimics the action profile of endogenous basal insulin, providing blood glucose control for close to 24 h with a once-daily dose [7]. A large body of clinical trial data has demonstrated the advantages of insulin therapy with insulin glargine in combination with OADs in patients with type 2 diabetes compared with NPH insulin [10–13]. The aim of the present observational study was to examine the initiation of insulin glargine therapy to support OAD treatment in a large patient population under everyday conditions and without the controlled settings of a clinical trial.

Methods

Study Design

This was a 9-month, open-label, uncontrolled, multicentre, observational study assessing the efficacy and safety of initiating insulin glargine in patients with type 2 diabetes inadequately controlled on OADs in everyday practice in Germany. Treatment choices and dosing adjustments, including any changes to OADs, were made at the physician's discretion, reflecting everyday practice. After 9 months of observation, an extension of up to 20 months was offered to participating physicians.

This type of study is regulated by the German Drug Law [Arzneimittelgesetz (AMG)] §67(6) and is primarily intended to gather knowledge about the safety and efficacy of marketed drugs in daily practice. Owing to the non-interventional nature of the study, no ethical approval or informed patient consent was obtained, in accordance with local regulations (AMG). Participation in the study was voluntary. Participating general

practitioners (GPs) were asked to document their everyday experience in treating patients with insulin glargine in combination with OADs and received a small compensation for the documentation of each patient, which is common practice for this type of study.

Patient demographics, diabetes history (including prior use of OADs), key efficacy variables and adverse events (AEs) were recorded on documentation folders. Serious AEs (SAEs) were reported on a SAE form, which was faxed to the pharmacovigilance department of the manufacturer within 24 h, who then transmitted the information to the relevant authorities [Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)].

Patients and Study Conduct

Patients with type 2 diabetes inadequately controlled on OADs who had not received previous insulin treatment were eligible for documentation in this observational study. Patients were enrolled by GPs, internal specialists and diabetologists. In addition to their current OAD therapy, patients were treated with insulin glargine (100 IU/ml).

The following parameters were collected at baseline, after 3 and 9 months (endpoint) of therapy and, for those participating in the extension phase, at 20 months: HbA_{1c}, fasting blood glucose (FBG), daily insulin dose and body mass index (BMI). All AEs occurring during the course of the observational period were documented.

Statistical Analysis

According to a predefined statistical analysis plan, the statistical analyses were descriptive and interpreted in an explorative manner. Plausibility checks were performed for demographic data, HbA_{1c}, FBG and BMI values, according to previously defined criteria. A sub-analysis was performed to determine changes in HbA_{1c}, FBG and BMI according to different baseline BMI groups.

Absolute and relative frequencies were calculated for qualitative variables and adjusted relative frequencies were calculated for variables with missing data points. For all quantitative variables with a baseline and at least one postbaseline data point, the mean, s.d., median, first and third quartiles, and first and ninety-ninth percentiles were calculated and the difference between baseline and endpoint analysed. Data analysis was performed using the statistical software package SAS® version 8.02 for Windows (SAS Inc., Cary, NJ, USA).

Table 1 Baseline characteristics of the total cohort and the patients enrolled in the 20-month extension study

Characteristic	Total cohort (n = 12,216)		Patients enrolled in the 20-month extension (n = 2721)	
	Number of subjects	Value*	Number of subjects	Value*
Age	12,117	63.9 ± 11.3 years	2702	63.8 ± 11.3 years
Male/female	12,148	6094/6054	2708	1382/1326
Body mass index	11,090	29.0 ± 4.7 kg/m ²	2016	29.0 ± 4.7
Duration of diabetes (years)				
>5	5683	47%	1300	48%
1-5	4803	39%	1038	38%
<1	1220	10%	255	9%
Newly diagnosed	439	4%	106	4%
HbA _{1c}	11,511	8.7 ± 1.4%	2374	8.7 ± 1.4%
Fasting blood glucose	12,100	202 ± 56 mg/dl (11.2 ± 3.1 mmol/l)	2527	202 ± 56 mg/dl (11.2 ± 3.1 mmol/l)

*Data are mean ± s.d. unless otherwise specified.

Results

Population and Baseline Characteristics

Of the 12,266 patients enrolled in the study, data were collected for 12,216 patients at 3 months and 6576 patients at 9 months. Patient baseline characteristics are summarized in table 1. At baseline, 46% of patients were aged ≥66 years and 50% were male. In the population of patients for whom the information was available, 98% had not received prior insulin therapy. A total of 93% (n = 11,296) of patients used OADs prior to the study, with the majority (72.1%) using sulphonylureas, 58.2% using biguanides, 10.2% using alpha-glucosidase inhibitors, 1.5% using thiazolidinediones and 7.6% using other OADs.

The distribution of patients in each of the subanalysis groups based on BMI was as follows: 1891 patients (15.5%) with BMI <25 kg/m²; 5355 patients (43.8%) with BMI ≥25 kg/m² and <30 kg/m²; 2789 patients (22.8%) with BMI ≥30 kg/m² and <35 kg/m²; 1055

patients (8.6%) with BMI ≥35 kg/m² [data missing for 1126 patients (9.2%)].

Efficacy

Glycaemic control improved after the initiation of add-on insulin glargine therapy. Both mean HbA_{1c} and FBG levels decreased from baseline after 3 and 9 months of treatment (table 2). Significantly, patients achieved mean HbA_{1c} levels of 7.0 ± 1.0% after 9 months of treatment. The results were comparable in both the total cohort and the population of patients with data available for baseline, 3 and 9 months (table 2). Furthermore, when the data were analysed according to the BMI subgroups, the results for HbA_{1c} and FBG were consistent with those seen for the whole population of patients for whom data was available at 9 months (n = 4975; table 3).

The insulin glargine dose increased by 5.6 IU over the course of the study, from a mean starting dose of

Table 2 Changes in glycaemic control after initiation of add-on insulin glargine therapy after 3 and 9 months in the total cohort and the completed population

	Total cohort		Population with data available at baseline, 3 and 9 months	
	n	Value	n	Value
HbA _{1c} (%)				
Baseline	11,511	8.7 ± 1.4	5729	8.7 ± 1.4
3 months	11,296	7.2 ± 0.9		7.2 ± 0.9
9 months	6031	7.0 ± 1.0		7.0 ± 1.0
Fasting blood glucose, mg/dl (mmol/l)				
Baseline	12,100	202 ± 56 (11.2 ± 3.1)	6180	203 ± 56 (11.3 ± 3.1)
3 months	11,872	133 ± 33 (7.4 ± 1.8)		133 ± 33 (7.4 ± 1.8)
9 months	6335	131 ± 35 (7.3 ± 1.9)		131 ± 35 (7.3 ± 1.9)

Table 3 Mean \pm s.d. outcome measures by body mass index (BMI) for patients in the total cohort for whom data were available at 9 months

	BMI category				
	All patients	<25 kg/m ²	≥ 25 to <30 kg/m ²	≥ 30 to <35 kg/m ²	≥ 35 kg/m ²
HbA _{1c} (%)					
n	5844	939	2551	1313	539
Baseline	8.7 \pm 1.4	8.5 \pm 1.4	8.6 \pm 1.3	8.8 \pm 1.4	8.9 \pm 1.6
9 months	7.0 \pm 1.0	6.9 \pm 1.0	7.0 \pm 0.9	7.1 \pm 1.0	7.2 \pm 1.1
Change from baseline at 9 months	-1.6	-1.6	-1.6	-1.7	-1.8
Fasting blood glucose, mg/dl (mmol/l)					
n	6289	1017	2749	1411	569
Baseline	202 \pm 56 (11.2 \pm 3.1)	201 \pm 60 (11.2 \pm 3.3)	199 \pm 52 (11.1 \pm 2.9)	207 \pm 57 (11.5 \pm 3.1)	211 \pm 64 (11.7 \pm 3.6)
9 months	131 \pm 35 (7.3 \pm 1.9)	128 \pm 35 (7.1 \pm 2.0)	130 \pm 32 (7.2 \pm 1.8)	133 \pm 34 (7.4 \pm 1.9)	138 \pm 39 (7.7 \pm 2.2)
Change from baseline at 9 months	-71 (-3.9)	-73 (-4.1)	-70 (-3.9)	-74 (-4.1)	-73 (-4.1)
Insulin glargine dose (IU)					
n	6356	1035	2788	1413	574
Starting dose	13.8 \pm 7.0	12.9 \pm 6.2	13.4 \pm 6.4	14.4 \pm 7.2	15.3 \pm 8.2
9 months	20.3 \pm 9.6	18.5 \pm 8.3	19.7 \pm 8.9	21.2 \pm 9.5	23.4 \pm 11.9
Change from starting dose at 9 months	+6.5	+5.6	+6.3	+6.8	+8.1

13.8 \pm 6.9 to 19.4 \pm 9.1 IU after 9 months (n = 11,866). As expected, the starting dose of insulin glargine was higher in patients with a greater BMI, but the increase in the insulin glargine dose during the study was consistent in all BMI categories (table 3).

A trend of decreasing BMI values was observed in the overall study population, from a mean of 29.0 \pm 4.7 kg/m² at baseline (n = 11,090) to 28.7 \pm 4.5 kg/m² after 3 months (n = 10,692) and 28.5 \pm 4.8 kg/m² after 9 months (n = 5324). When the change in BMI was analysed by BMI subgroup, a reduction in BMI in each of the subgroups of patients with BMI values ≥ 25 kg/m² was revealed. Mean BMI values increased slightly (+0.9 kg/m²) in patients with BMI <25 kg/m² (figure 1).

Safety

A total of 214 AEs were reported in 142 patients (1.2%) of which only 146 were considered SAEs. There were 47 reports of adverse drug reactions in 26 patients (0.2%), of which 19 events in 16 patients (0.1%) were due to hypoglycaemia.

Extension Study

In the 20-month extension of the original study, data were available for 2721 patients. Baseline characteristics of the patients in the extension study did not differ significantly from those of patients in the total cohort (n = 12,216; table 1). For patients with both baseline and 20-month follow-up data, the HbA_{1c} (n = 2374) and FBG (n = 2527) levels were comparable with those observed after 9 months of treatment in these patients (table 4). In addition, HbA_{1c} and FBG 20-month data analysed according to the BMI subgroups were consistent with those seen at 9 months (table 4). The starting dose of insulin glargine dose increased after 9 months

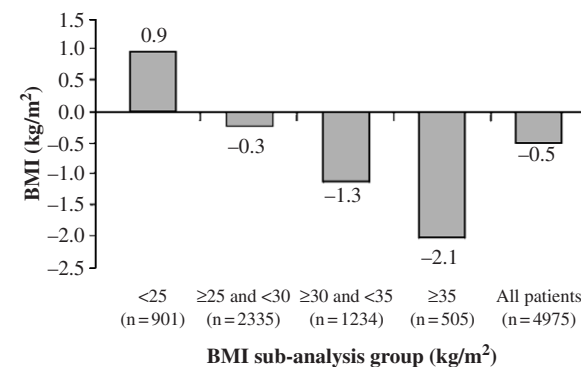


Fig. 1 Change in body mass index (BMI) from baseline to endpoint in BMI subgroups.

Table 4 Mean \pm s.d. outcome measures for patients in the extension study for whom data were available at baseline and 20 months

	BMI category				
	All patients	<25 kg/m ²	≥ 25 to <30 kg/m ²	≥ 30 to <35 kg/m ²	≥ 35 kg/m ²
HbA _{1c} (%)					
n*	2374	373	1048	535	227
Baseline	8.7 \pm 1.4	8.4 \pm 1.4	8.6 \pm 1.4	8.8 \pm 1.3	8.9 \pm 1.6
9 months	7.0 \pm 0.9	6.9 \pm 1.0	6.9 \pm 0.9	7.1 \pm 0.9	7.2 \pm 1.0
20 months	7.0 \pm 1.0	6.9 \pm 0.9	6.9 \pm 1.0	7.1 \pm 0.9	7.2 \pm 1.1
Change from baseline at 20 months	-1.6	-1.5	-1.7	-1.7	-1.7
Fasting blood glucose, mg/dl (mmol/l)					
n [†]	2527	402	1112	569	245
Baseline	202 \pm 56 (11.2 \pm 3.1)	197 \pm 57 (10.9 \pm 3.2)	199 \pm 53 (11.1 \pm 2.9)	206 \pm 54 (11.4 \pm 3.0)	211 \pm 69 (11.7 \pm 3.8)
9 months	130 \pm 33 (7.2 \pm 1.8)	125 \pm 36 (6.9 \pm 2.0)	128 \pm 30 (7.1 \pm 1.7)	132 \pm 34 (7.3 \pm 1.9)	138 \pm 37 (7.7 \pm 2.1)
20 months	131 \pm 37 (7.3 \pm 2.1)	124 \pm 35 (6.9 \pm 1.9)	129 \pm 35 (7.2 \pm 1.9)	134 \pm 36 (7.4 \pm 2.0)	138 \pm 40 (7.7 \pm 2.2)
Change from baseline at 20 months	-71 (-3.9)	-73 (-4.1)	-70 (-3.9)	-72 (-4.0)	-74 (-4.1)
Insulin glargine dose (IU)					
n [‡]	2487	403	1088	557	233
Starting dose	14.2 \pm 7.2	12.9 \pm 6.3	13.9 \pm 6.5	15.1 \pm 7.9	15.9 \pm 8.4
9 months	20.2 \pm 9.5	18.6 \pm 8.1	19.3 \pm 9.1	21.3 \pm 9.3	23.8 \pm 11.0
20 months	22.3 \pm 9.9	20.5 \pm 9.4	21.6 \pm 9.0	23.1 \pm 9.7	25.7 \pm 11.8
Change from starting dose at 20 months	+8.1	+7.6	+7.7	+8.0	+9.8

*Data missing for 191 patients.

†Data missing for 199 patients.

‡Data missing for 206 patients.

(+6.0 IU) and continued to increase at 20 months (+8.1 IU; $n = 2487$; table 4). An overall decrease in patient BMI was observed, from 29.0 ± 4.7 to 28.6 ± 4.7 kg/m² at 9 months and 28.7 ± 4.7 kg/m² at 20 months (-0.4 kg/m² after 20 months; $n = 2016$).

Discussion

Our findings from 12,216 patients demonstrated that in everyday clinical practice, patients with type 2 diabetes inadequately controlled on OADs benefit from the addition of basal insulin treatment with insulin glargine. Furthermore, the results from this observational study support the data from previous clinical trials [10–13].

In particular, the reductions in mean HbA_{1c} (-1.7%) and FBG [-71 mg/dl (-3.9 mmol/l)] observed after 9 months of treatment in this diverse population are consistent with the improved glycaemic control reported in clinical studies of patients with type 2 diabetes. The improvements in glycaemic control were achieved without any safety issues, with only 1.2% of patients reporting AEs during the 9-month observation period. In addition, the results of the 2721 patients enrolled in the extension study suggested that the levels of glycaemic control achieved after 9 months of treatment could be maintained for up to 20 months.

It is also of interest to note that the improved glycaemic control was associated with a decrease in BMI in the majority of patients. In clinical studies, the body weight of patients with type 2 diabetes treated with insulin glargine has been shown to increase to a similar extent or less compared with patients treated with NPH insulin [9–13]. However, the findings of this observational study demonstrate that the use of insulin glargine in combination with OADs in everyday practice improves glycaemic control without an increase in weight in patients with type 2 diabetes inadequately controlled on OAD regimens. The reason for this difference remains to be further investigated, but may be associated with the insulin dose.

In this study, insulin glargine dosing (with a mean daily dose of 20 IU after 9 months) was actually lower than in previous clinical studies (where the mean daily dose ranged from 23 to 47 IU) [9,13–15]. The starting dose of insulin glargine was higher in patients with a greater BMI, but the increase in insulin dose seen in the overall population was consistent across all BMI subgroups. This may reflect the treatment habits in everyday practice to introduce insulin at an early stage of the disease and therefore achieve glycaemic control targets with lower insulin doses. A recent clinical trial demonstrated how glycaemic control targets can be achieved

with a low insulin dose in patients at an early stage of type 2 diabetes [6].

Poor glycaemic control is associated with an increased risk of diabetic complications in type 2 diabetes [16] and HbA_{1c} levels of $<7\%$ have been recommended in order to prevent diabetic complications [17]. Achieving and maintaining good glycaemic control necessitates the use of insulin at an early stage of disease progression and the introduction of complex insulin regimens to insulin-naïve patients may lead to low treatment compliance. Therefore, the simple treatment regimen of insulin glargine combined with OADs is one option to facilitate early insulin treatment and has been shown to provide a greater decrease in HbA_{1c} levels compared with an insulin regimen using premixed insulin [14]. A wide range of clinical studies have demonstrated that target HbA_{1c} levels can be achieved with insulin glargine without an increased risk of hypoglycaemia [18], but less data are available to show the long-term outcome of metabolic control outside of the clinical setting. In this study we showed that patients can achieve mean HbA_{1c} levels of 7.0% after 9 months of treatment, supporting a role for insulin glargine in attaining glycaemic targets in everyday clinical practice.

The purpose of observational studies is to examine the use of a medication in everyday practice. Contrary to prevailing views, well designed observational studies provide an important and valid tool in assessing the magnitude of treatment effects [19,20]. Such studies can be used to confirm the efficacy and safety of a therapeutic agent when used in a broad population without influencing the normal practice of GPs and their patients. This type of study allows conclusions to be made on the applicability of a particular therapy outside the setting of a clinical trial; in everyday practice, there may be poor compliance and widely variable patient characteristics, such as the number of comorbidities and concomitant medications. The non-interventional nature of this study provides the possibility to detect differences between the controlled use of insulin glargine as prescribed in clinical trials and its actual application by physicians and patients in everyday life.

This was the first study performed to assess the use of insulin glargine in a real-life setting in a large cohort of patients with type 2 diabetes. The population enrolled in this long-term study is typical of the general population of patients with type 2 diabetes in an outpatient setting in Germany. The majority of patients were ≥ 60 years old and overweight. The high blood glucose levels reported at the start of the study reflected the patients' poor glycaemic control on OAD therapy and indicated the need for a change in their current treatment regimens.

However, although observational studies provide additional data to support the results of randomized clinical trials, there are limitations to the conclusions that can be drawn from such uncontrolled, non-randomized studies. Due to the non-interventional documentation of everyday routine, missing data occur if the treatment habits of the participant differ from the schedule of the documentation record. Additionally, the number of documentations returned depends on the willingness and cooperation of the participating GPs to continue the documentation for the observation period. In this study, 12,266 documentations were received after 3 months and 6576 documentations were received after 9 months of observation. There was no information about patients for whom documentation was returned after 3 months but not after 9 months and conclusions could only be drawn from the data that were received. Despite these limitations, the benefit of 'real world' observational studies to the practising physician should not be underestimated.

In conclusion, patients with type 2 diabetes inadequately controlled on OAD regimens alone can benefit from the addition of insulin glargine to their current therapy in everyday practice. Insulin glargine therapy in these patients was found to be safe and resulted in improved glycaemic control without an increase in BMI.

Acknowledgements

This study was supported by Aventis Pharma Deutschland GmbH, a company of the sanofi-aventis group. We would like to thank all of the more than 2200 investigators for their commitment to this study.

Selected 9-month data from this manuscript were published in German (*Diabetes und Stoffwechsel* 2005; 14: 13–18). Data from this manuscript have also been published in abstract form (*Diabetes* 2005; 54(Suppl1): A143 [Abstract 579]; *Diabetologia* 2005; 48(Suppl1): A306 [Abstract 841]; *Diabetes* 2004; 53(Suppl 2): A146 [Abstract 614]; *Diabetologia* 2004; 47(Suppl 1): A268 [Abstract 739]); *Diabetes und Stoffwechsel* 2005; 14(Suppl1): 96 [Abstract: p-212], 40th Jahrestagung Dtsch Diabetes Ges, Berlin, May 2005) and presented as posters at the American Diabetes Association 2004 and 2005, the European Association for the Study of Diabetes 2004 and 2005, and the Deutsche Diabetes Gesellschaft 2005 congresses.

References

1 Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004; **27**: 1047–1053.

- 2 Hauner H, Koster I, von Ferber L. Prevalence of diabetes mellitus in Germany 1998–2001. Secondary data analysis of a health insurance sample of the AOK in Hesse/KV in Hesse. *Dtsch Med Wochenschr* 2003; **128**: 2632–2637.
- 3 Chehade JM, Mooradian AD. A rational approach to drug therapy of type 2 diabetes mellitus. *Drugs* 2000; **60**: 95–113.
- 4 Rosenstock J. Basal insulin supplementation in type 2 diabetes; refining the tactics. *Am J Med* 2004; **116** (Suppl. 3A): 10S–16S.
- 5 Home P, Boulton A, Jimenez J, Landgraf R, Osterbrink B, Christiansen J, on behalf of the Worldwide Initiative for Diabetes Education (WorldWIDE). Issues relating to the early or earlier use of insulin in type 2 diabetes. *Pract Diabetes Int* 2003; **20**: 63–71.
- 6 Fach E-V, Busch K, Anderesi Z, Schweitzer M-A, Standl E. HOE901/4009 Study Group: efficacy of insulin glargine in Type 2 diabetes: effect at different stages of diabetes. *Diabetes* 2004; **53**: A124 [Abstract 524-P].
- 7 Heinemann L, Linkeschova R, Rave K, Hompesch B, Sedlak M, Heise T. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care* 2000; **23**: 644–649.
- 8 Lepore M, Pampanelli S, Fanelli C *et al*. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes* 2000; **49**: 2142–2148.
- 9 Yki-Järvinen H, Dressler A, Ziemer M. Less nocturnal hypoglycemia and better post-dinner glucose control with bedtime insulin glargine compared with bedtime NPH insulin during insulin combination therapy in type 2 diabetes. HOE 901/3002 Study Group. *Diabetes Care* 2000; **23**: 1130–1136.
- 10 Riddle M, Rosenstock J, Gerich J; Insulin Glargine 4002 Study Investigators. The Treat-to-Target Trial: randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care* 2003; **26**: 3080–3086.
- 11 Rosenstock J, Schwartz S, Clark CJ, Park G, Donley D, Edwards M. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE 901) and NPH insulin. *Diabetes Care* 2001; **24**: 631–636.
- 12 Massi Benedetti M, Humburg E, Dressler A, Ziemer M. A one-year, randomised, multicentre trial comparing insulin glargine with NPH insulin in combination with oral agents in patients with Type 2 diabetes. *Horm Metab Res* 2003; **35**: 189–196.
- 13 Fritsche A, Schweitzer M, Haring H-U; 4001 Study Group. Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial. *Ann Intern Med* 2003; **138**: 952–959.

- 14 Janka H, Plewe G, Kliebe-Frisch C, Schweitzer M, Yki-Järvinen H. Starting insulin for Type 2 diabetes with insulin glargine added to oral agents vs twice-daily NPH premixed insulin alone. *Diabetes* 2004; **53**: A130 [Abstract 548–P].
- 15 Yki-Jarvinen H. Combination therapy with insulin and oral agents: optimizing glycemic control in patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev* 2002; **18** (Suppl. 3): S77–S81.
- 16 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998; **352**: 837–853.
- 17 American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care* 2004; **27** (Suppl. 1): S15–S35.
- 18 Dunn CJ, Plosker GL, Keating GM, McKeage K, Scott LJ. Insulin glargine: an updated review of its use in the management of diabetes mellitus. *Drugs* 2003; **63**: 1743–1778.
- 19 Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. *N Engl J Med* 2000; **342**: 1878–1886.
- 20 Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; **342**: 1887–1892.