Basal Insulin Therapy in Type 2 Diabetes

28-week comparison of insulin glargine (HOE 901) and NPH insulin

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OBJECTIVE — To determine the safety and efficacy of the long-acting analog insulin glargine compared with NPH insulin in patients with type 2 diabetes who were previously treated with insulin alone.

RESEARCH DESIGN AND METHODS — A total of 518 subjects with type 2 diabetes who were receiving NPH insulin with or without regular insulin for postprandial control were randomized to receive insulin glargine (HOE 901) once daily ($n = 259$) or NPH insulin once or twice daily ($n = 259$) for 28 weeks in an open-label, multicenter trial. Doses were adjusted to obtain target fasting glucose <6.7 mmol/l. At study end point, the median total daily insulin dose in both treatment groups was 0.75 IU/kg.

RESULTS — The treatment groups showed similar improvements in HbA_{1c} from baseline to end point on intent-to-treat analysis. The mean change (means $\pm$ SD) in HbA_{1c} from baseline to end point was similar in the insulin glargine group ($-0.41 \pm 0.1\%$) and the NPH group ($-0.59 \pm 0.1\%$) after patients began with an average baseline HbA_{1c} of ~8.5%. The treatments were associated with similar reductions in fasting glucose levels. Overall, mild symptomatic hypoglycemia was similar in insulin glargine subjects (61.4%) and NPH insulin subjects (66.8%). However, nocturnal hypoglycemia in the insulin glargine group was reduced by 25% during the treatment period after the dose-titration phase (26.5 vs. 35.5%, $P = 0.0136$). Subjects in the insulin glargine group experienced less weight gain than those in the NPH group (0.4 vs. 1.4 kg, $P < 0.0007$).

CONCLUSIONS — In patients with type 2 diabetes, once-daily bedtime insulin glargine is as effective as once- or twice-daily NPH in improving and maintaining glycemic control. In addition, insulin glargine demonstrates a lower risk of nocturnal hypoglycemia and less weight gain compared with NPH insulin.

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Insulin treatment can improve and maintain glycemic control, preventing long-term complications in type 2 diabetes (1–3). Over time, most patients with type 2 diabetes experience progressive β-cell dysfunction and will require insulin therapy, either alone or in combination with oral agents, for satisfactory glycemic control (4). Attempts to mimic physiologic patterns of basal insulin secretion have been difficult because most currently available insulins have disadvantages, including variable absorption, pronounced peaks after injection, and abbreviated durations of action (5–8).

The novel recombinant insulin analog insulin glargine (HOE 901; 21^A-Gly-30^Ba-L-Arg-30^Bb-L-Arg-human insulin) is a modification of human insulin in which two arginines are added to the B-chain and glycine is substituted for asparagine at the A21 position of the insulin molecule. These changes cause a shift of the isoelectric point to a neutral pH (9–11), precipitation at physiologic tissue pH, and increased hexamer stability, resulting in delayed absorption and a flat profile after injection, compared with the shorter duration of action and early peak of NPH insulin (9–12). Short-term clinical trials in patients with type 1 and type 2 diabetes suggest that once-daily insulin glargine as basal insulin replacement is safe and at least as effective as once- or twice-daily NPH insulin in maintaining glycemic control (13–17). In a recent European multicenter study, insulin-naïve patients who were taking oral agents were initiated on insulin therapy while continuing oral agents. Patients taking insulin glargine experienced significantly less nocturnal hypoglycemia and better postdinner glucose control than patients taking NPH, demonstrating advantages of insulin glargine in combination therapy despite low insulin doses (18).

In the present study, we compared the safety and effectiveness of once-daily bedtime insulin glargine with once- or twice-daily NPH insulin in patients with type 2 diabetes who were not taking oral agents and who had previously received basal insulin with or without regular insulin for postprandial glycemic control.

RESEARCH DESIGN AND METHODS — The study was a 59-center, randomized, open-label comparison of insulin glargine and NPH insulin in patients with type 2 diabetes, aged 40–80 years, who had been receiving insulin treatment for ≥3 months. HbA_{1c} was 7.0–12.0% and BMI was <40.0 kg/m². Patients were excluded if they had significant hepatic or renal impairment or had received treatment with an oral antidiabetic drug within 3 months prior. Written

informed consent was obtained from patients before enrollment.

The study included a 1- to 4-week screening phase during which subjects continued their current NPH insulin and regular insulin treatments, followed by a 28-week treatment phase. They were instructed in the use of the glucose meter (One Touch Profile System; Lifescan, Milpitas, CA) for self-monitored blood glucose assessment. Subjects were then randomized to receive insulin glargine subcutaneously once daily at bedtime or NPH insulin subcutaneously once daily (at bedtime) or twice daily (morning and bedtime), depending on their prior treatment at baseline. Subjects previously using NPH insulin two or more times daily received NPH twice daily during the treatment period. Insulin glargine is a clear solution and is easily distinguished from NPH insulin, requiring an open-label design. Subjects continued to administer premeal regular insulin as indicated. To preserve its pharmacokinetic/pharmacodynamic profile, insulin glargine cannot be mixed with other insulin solutions.

Insulin glargine (Aventis Pharmaceuticals, Frankfurt, Germany) was supplied in vials containing 5 ml solution (1 ml containing 100 IU insulin). NPH and regular human insulin (Eli Lilly, Indianapolis, IN) were supplied in vials containing 10 ml suspension (1 ml containing 100 IU insulin). Subjects previously taking NPH insulin and randomized to insulin glargine were switched from their previous once-daily basal insulin dose on a unit-for-unit basis. Subjects previously using twice-daily NPH and randomized to receive insulin glargine were advised to reduce insulin glargine dosage 10% compared with total NPH dosage. Thereafter, insulin glargine and NPH insulin doses were individually titrated based on a target fasting plasma glucose (FPG) of 4.4–7.8 mmol/l. Evening doses were increased if FPG was ≥10.0 mmol/l on three consecutive measurements unless nocturnal hypoglycemia had occurred. Targets for use of regular insulin were premeal blood glucose 4.4–7.8 mmol/l and bedtime blood glucose 6.7–10.0 mmol/l.

The primary efficacy variable was change in HbA_{1c} between baseline and study end point. Other efficacy measures included comparison of changes from baseline for fasting blood glucose (FBG) at weeks 8, 20, and 28 and at study end point, consisting of the mean self-monitored blood glucose values on the 7 consecutive days before the visit and frequency and severity of hypoglycemia. HbA_{1c} was measured in whole blood by an affinity chromatographic method by the Diabetes Diagnostic Laboratory (University of Missouri, Columbia, MO) and can be referenced to the HbA_{1c} method used in the Diabetes Control and Complications Trial. Hypoglycemia was defined symptomatically and by a blood glucose level <2.8 mmol/l. Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia in which the subject required assistance of another person and was either accompanied by a blood glucose level <2.0 mmol/l or had prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycemia was defined as that occurring while the subject was asleep between bedtime after the evening injection and before getting up in the morning (before morning determination of FBG and morning injection).

Statistical analysis

All analyses were based on intent to treat and included all subjects with postbaseline data. Differences in HbA_{1c} between treatment groups were assessed by analysis of covariance (ANCOVA) using change from baseline to end point as the dependent variable, with treatment and pooled center as fixed effects and the corresponding baseline value as a covariate. The difference in mean change from baseline between treatment groups was estimated using adjusted mean values along with the associated standard error and 95% CI from the ANCOVA model. The study was designed to provide 90% power to detect an average difference of 0.5% in HbA_{1c} between treatment groups. Similar methods were used for analysis of FBG. Incidences of symptomatic, nocturnal symptomatic, and severe symptomatic hypoglycemia were compared using the Cochran-Mantel-Haenszel test stratified by pooled center. For purposes of analyzing hypoglycemia, the first month of treatment was considered a dose-titration phase because of the anticipated need for dosage modification in subjects receiving insulin glargine. Baseline variables were compared using analyses of variance and Cochran-Mantel-Haenszel tests stratified by pooled center. All statistical tests

Table 1—Demographics and baseline characteristics of subjects randomized and treated

	Insulin glargine	NPH insulin
n	259	259
M/F	150 (57.9)/109 (42.1)	161 (62.2)/98 (37.8)
Age (years)	59.5 ± 9.7	59.2 ± 9.9
BMI (kg/m^2)	30.7 ± 5.0	30.4 ± 5.1
Race/ethnicity		
White	208 (80.6)	209 (80.7)
Black	40 (15.5)	36 (13.9)
Hispanic	22 (8.5)	22 (8.5)
Reported prior basal insulin schedule		
Once daily	50 (19.3)	50 (19.3)
Twice daily	205 (79.1)	204 (78.7)
More than twice daily	4 (1.5)	5 (1.9)
Prior regular insulin use	161 (62.1)	167 (64.4)
Diabetes history		
Duration (years)	13.4 ± 8.3	14.1 ± 9.0
Age at onset (years)	46.7 ± 9.4	45.7 ± 10.7
Insulin treatment (years)	8.4 ± 6.9	8.3 ± 7.6
C-peptide (mmol/l)	0.6 ± 0.4	0.6 ± 0.5
History of retinopathy	124 (47.9)	147 (56.8)
Metabolic control		
HbA_{1c} (%)	8.6 ± 1.2	8.5 ± 1.2
Fasting plasma glucose (mmol/l)	10.6 ± 3.9	11.1 ± 4.3
Fasting blood glucose (mmol/l)	9.1 ± 2.4	9.2 ± 2.4
Symptomatic hypoglycemia during screening phase	66 (25.5)	77 (29.7)

Data are n (%) or means ± SD.

were two-sided and performed at a significance level of $\alpha = 5\%$ unless otherwise indicated.

RESULTS

Subjects

A total of 518 subjects were randomized and received study treatment. Premeal regular insulin was reported to be used by 62% of subjects (161 of 259) randomized to insulin glargine and 64% of subjects (167 of 259) randomized to NPH. Of 259 subjects randomized to once-daily bedtime insulin glargine, 207 (80%) and 52 (20%) subjects were stratified for the purpose of subsequent analysis to subgroups of more-than-once-daily and once-daily basal insulin, respectively, based on their prestudy regimen. Of 259 subjects randomized to NPH insulin, 211 (81.5%) received twice-daily morning and bedtime treatment and 48 (18.5%) received once-daily bedtime treatment. There were no significant differences between groups with regard to demographics, diabetic disease characteristics, or metabolic control at baseline (Table 1).

A total of 28 insulin glargine recipients and 21 NPH recipients withdrew from the study after beginning treatment; in 13 insulin glargine subjects and 9 NPH subjects, the reason was the subject's desire to discontinue or loss to follow-up. Nine insulin glargine subjects (3.5%) and seven NPH insulin subjects (2.7%) discontinued treatment because of adverse events.

Insulin doses

Median daily doses of basal and total insulin for treatment groups, according to prestudy basal insulin regimen, are shown in Fig. 1. In the small number of subjects treated prestudy with once-daily basal insulin, the median basal dose and the total insulin dose increased slightly over the duration of the study (Fig. 1*A*). In subjects treated prestudy with more-than-once-daily basal insulin, the daily basal insulin dose was 8.4 IU less during the first week of the study than at baseline in the once-daily insulin glargine group, whereas the dose was 2.0 IU higher in the twice-daily NPH group. Subsequently, the daily basal insulin dose in the insulin glargine group was titrated upward, but at week 28, the median daily dose was still 4.4 IU less than the baseline dose (Fig. 1*B*). At study end point, subjects treated
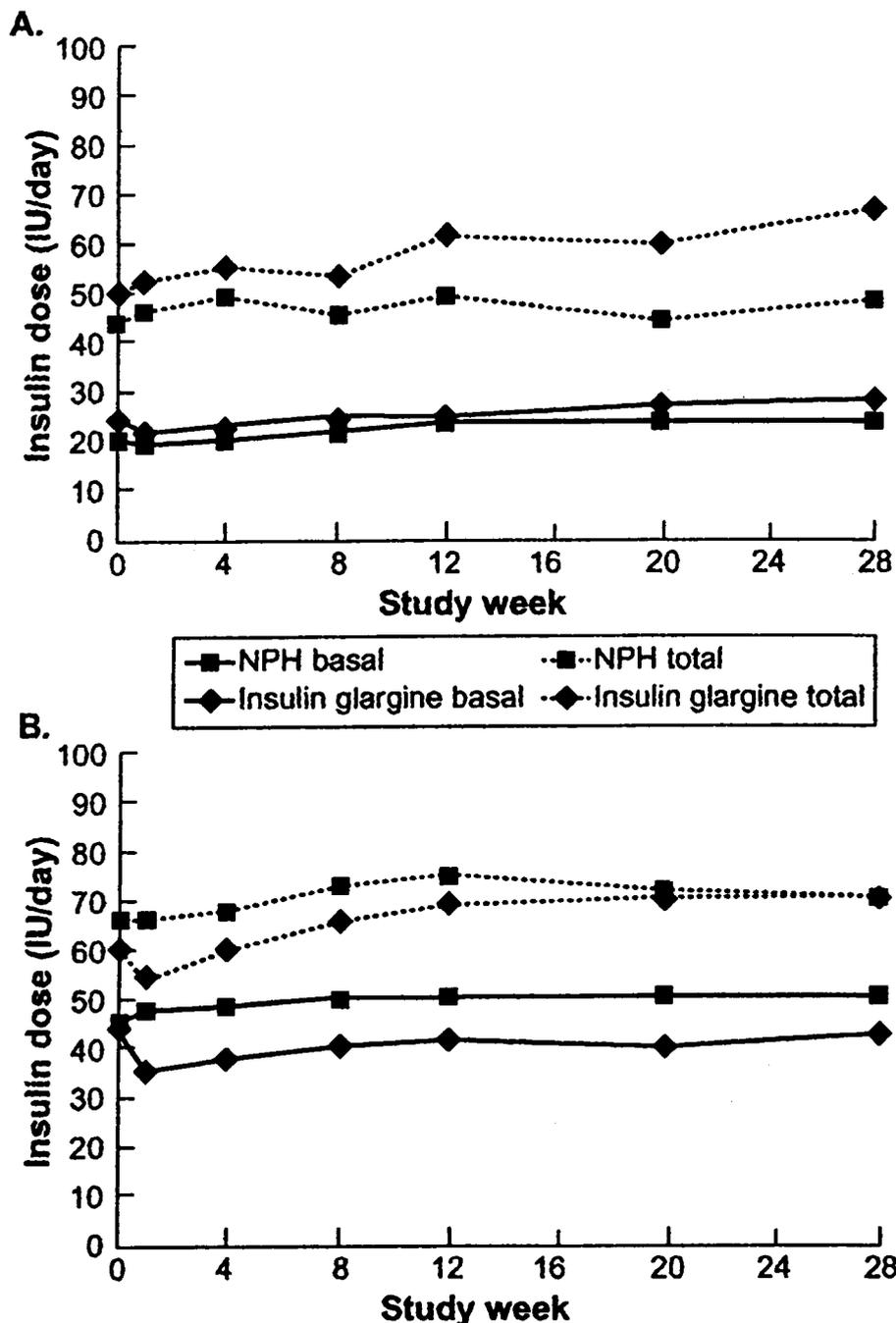

Figure 1—*Summary of the median daily basal insulin dose and the total daily insulin dose (basal plus regular insulin) for insulin glargine and NPH insulin in subjects treated with (A) a prior once-daily basal insulin regimen (insulin glargine, n = 51; NPH, n = 48) and (B) a prior more-than-once-daily basal insulin regimen (insulin glargine, n = 202; NPH, n = 211).*

with insulin glargine once daily were receiving a median of 40 IU basal insulin per day at bedtime. Subjects treated with NPH twice daily were receiving a median dose of 23 IU basal insulin per day at bedtime and taking the rest of their daily dose in the morning. The median daily dose of regular insulin in subjects receiving insu- lin glargine increased more than in subjects receiving NPH; at the end of the study, the median daily regular insulin dose was 6.0 IU higher than baseline in the subgroup of insulin glargine subjects previously on more-than-once-daily basal insulin. At end point, the median total daily insulin dose was the same in the in-
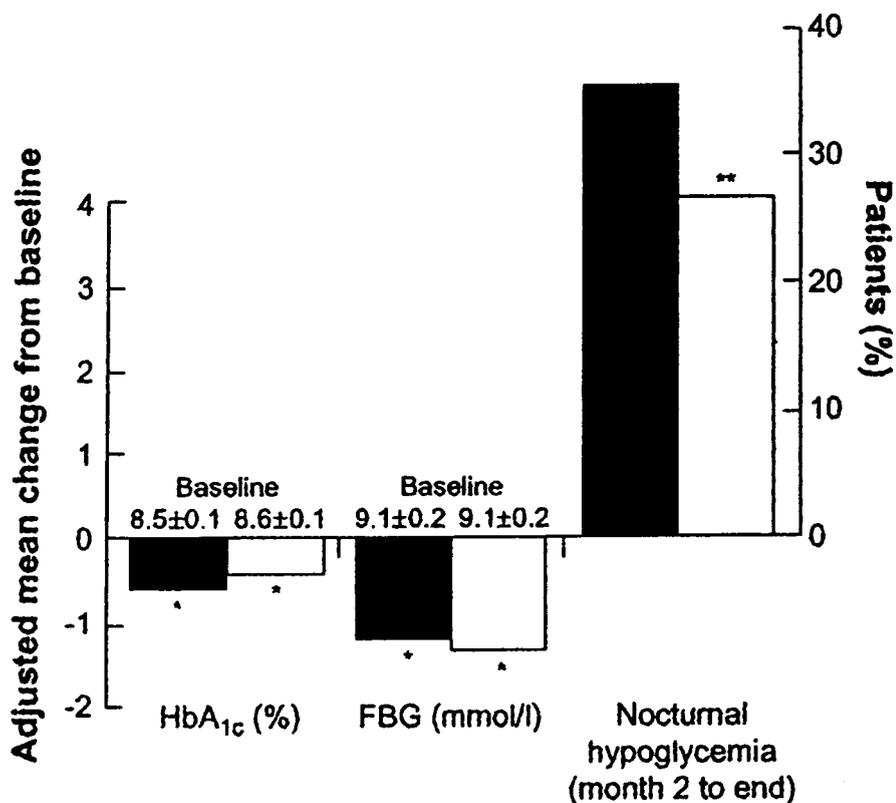
Figure 2—*Summary of effects of insulin glargine and NPH on HbA₁c, FBG, and nocturnal hypoglycemia. ■, NPH; □, insulin glargine. *P < 0.01; **P < 0.02 (insulin glargine vs. NPH).*

sulin glargine treatment group and the NPH treatment group (0.75 IU/kg).

Efficacy measures
Glycohemoglobin. The insulin glargine and NPH groups had similar (means ± SD) baseline HbA_{1c} levels (8.6 ± 0.1% and 8.5 ± 0.1%, respectively). Reductions in HbA_{1c} from baseline to end point were significant in both groups ($P = 0.0001$). At the study end point, there was no relevant difference in changes in adjusted mean HbA_{1c} between the study groups. The 95% CI for the difference between treatments in HbA_{1c} (0.00, 0.35) excludes values that would indicate inferiority of insulin glargine treatment (Fig. 2). No significant difference between treatments was observed when results were analyzed by prior basal insulin regimen.
FBG. Change in FBG from baseline was significant at end point in both groups ($P = 0.0001$). The insulin glargine and NPH treatment groups were similar at baseline (9.1 ± 0.2 mmol). No difference was observed between the treatment groups in changes in adjusted mean FBG or between the prior once-daily and twice-daily subgroups. Similar proportions of

subjects receiving insulin glargine (29.6%) and NPH (27.1%) achieved FBG <6.7 mmol/l by study end point.
Symptomatic hypoglycemia. Overall symptomatic hypoglycemia was reported in 159 subjects receiving insulin glargine (61.4%) and 173 subjects receiving NPH (66.8%). Blood glucose values were measured for 94.0% of symptomatic hypoglycemic episodes during treatment. We found that 17 (6.6%) subjects in the insulin glargine group had 42 episodes of hypoglycemia accompanied by a blood glucose value <2.0 mmol/l, compared with 27 (10.4%) subjects in the NPH group who reported 62 episodes ($P = 0.0553$).

Throughout the entire treatment period, insulin glargine was associated with significantly less nocturnal hypoglycemia than NPH ($P = 0.0160$). Only 81 (31.3%) insulin glargine subjects reported at least one episode of nocturnal hypoglycemia compared with 104 (40.2%) NPH subjects. A 25% reduction in nocturnal hypoglycemia was maintained with insulin glargine, even excluding the dose-titration phase from analysis, with 66 (26.5%) insulin glargine subjects and 92 (35.5%) NPH subjects reporting at least one episode of

nocturnal hypoglycemia from month 2 to study end ($P = 0.0136$) (Fig. 2).
Weight. Subjects treated with insulin glargine gained significantly less weight than subjects treated with NPH. Mean body weight increases from baseline to study end point were from 89.7 ± 17.4 to 90.0 ± 17.8 kg for insulin glargine subjects, and from 90.7 ± 17.8 to 92.1 ± 18.3 kg for NPH subjects (0.4 vs. 1.4 kg; $P = 0.0007$).

Safety
Nine insulin glargine subjects discontinued treatment because of adverse events. Only cellulitis at the injection site was considered related to study medication; it was attributed to poor injection technique. Seven NPH insulin subjects discontinued treatment because of adverse events; none were considered related to study medication. Treatment-related adverse events occurred in 27 (10.4%) insulin glargine subjects and 20 (7.7%) NPH insulin subjects. Mild pain at the injection site occurred more frequently with insulin glargine than with NPH insulin but did not result in discontinuation of treatment. The insulin glargine group had a significantly greater decrease in insulin antibody levels as shown by a tracer for either insulin glargine or human insulin antibodies.

CONCLUSIONS — A noteworthy difference between treatments in the current study is the significant 25% lower risk of nocturnal hypoglycemia associated with insulin glargine compared with NPH insulin. Although the overall incidence of symptomatic hypoglycemia was similar in the two treatment groups, nocturnal episodes from month 2 to the end of treatment were significantly lower in the insulin glargine group compared with the NPH group (26.5 vs. 35.5%). The lower risk of nocturnal hypoglycemia reflects the smooth, peakless activity profile of insulin glargine compared with the peak of NPH, which can result in maximum concentrations of insulin at night when NPH is given at bedtime. Severe hypoglycemia was observed in only one (0.4%) insulin glargine patient compared with six (2.3%) NPH insulin patients ($P = 0.0581$).

By study end point, the insulin glargine and NPH insulin groups showed similar significant decreases in HbA_{1c} (−0.41 and −0.59%, respectively). However, normal HbA_{1c} and fasting glucose levels were not achieved in most subjects in either treatment group, despite dose

titration throughout the study. This result may have been due to reluctance of the investigators and/or subjects to intensively titrate the insulin dose because of fear of hypoglycemia or weight gain. Indeed, hypoglycemia and weight gain were cited in the U.K. Prospective Diabetes Trial as key barriers to achieving normal glycemia (4).

Furthermore, the target FPG of 4.4–7.8 mmol/l with the recommendation to increase the evening insulin dose if FPG ≥10.0 mmol/l was perhaps set too high to achieve greater reductions in HbA_{1c} closer to the target of <7%. Future studies titrating to a lower target of FPG ≤5.6 mmol/l may result in greater reductions in HbA_{1c} and further uncover the potential for insulin glargine to yield less nocturnal hypoglycemia compared with NPH.

Insulin glargine treatment was associated with significantly less weight gain than NPH insulin treatment (0.40 vs. 1.40 kg). Presumably, the difference in weight gain despite comparable improvement in glycemic control reflects the less frequent hypoglycemia seen with insulin glargine, the correction of which requires supplemental caloric intake. Further long-term studies are required to assess the clinical relevance of the observed difference in weight gain. Incidence of treatment-related adverse events was similar in the treatment groups; injection site reactions were more common in insulin glargine recipients. The number of injection site reactions, particularly pain, reported in this group may reflect a bias resulting from the required open-label design or may be related to the insulin pH. No evidence of immunogenicity was observed with insulin glargine.

For patients who were transferred from a prestudy insulin regimen involving two or more daily injections to once-daily insulin glargine, the median dose was decreased 20% from 44.4 to 36.0 IU during the first week. Based on the results of the present study, it can be recommended that when transferring patients from a twice-daily NPH regimen, the dose of insulin glargine should be reduced by ~20% with careful titration according to the target FBG.

In summary, once-daily bedtime insulin glargine is as effective as once- or twice-daily NPH as basal insulin treatment in patients with type 2 diabetes who are currently receiving basal insulin with regular insulin for postprandial control.

Insulin glargine seems to have the advantage of reducing the frequency of nocturnal hypoglycemia, with a safety profile that is otherwise similar to NPH insulin.

APPENDIX

Investigators and locations

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