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

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Background: Patients with type 2 diabetes are often treated with oral antidiabetic agents plus a basal insulin.

Objective: To investigate the efficacy and safety of glimepiride combined with either morning or bedtime insulin glargine or bedtime neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes.

Design: Open-label, randomized, controlled trial.

Setting: 111 centers in 13 European countries.

Patients: 695 patients with type 2 diabetes who were previously treated with oral antidiabetic agents.

Intervention: Randomization to treatment with morning insulin glargine, bedtime NPH insulin, or bedtime insulin glargine for 24 weeks in addition to 3 mg of glimepiride. The insulin dose was titrated by using a predefined regimen to achieve fasting blood glucose levels of 5.56 mmol/L or lower (≤100 mg/dL).

Measurements: Hemoglobin A_{1c} values, blood glucose levels, insulin dose, and body weight.

Results: Hemoglobin A_{1c} levels improved by −1.24% (two-sided 90% CI, −1.10% to −1.38%) with morning insulin glargine, by −0.96% (CI, −0.81% to −1.10%) with bedtime insulin glargine, and by −0.84% (CI, −0.69% to −0.98%) with bedtime NPH insulin. Hemoglobin A_{1c} improvement was more pronounced with morning insulin glargine than with NPH insulin (0.40% [CI, 0.23% to 0.58%]; $P = 0.001$) or bedtime insulin glargine (0.28% [CI, 0.11% to 0.46%]; $P = 0.008$). Baseline to end-point fasting blood glucose levels improved similarly in all three groups. Nocturnal hypoglycemia was less frequent with morning (39 of 236 patients [17%]) and bedtime insulin glargine (52 of 227 patients [23%]) than with bedtime NPH insulin (89 of 232 patients [38%]) ($P < 0.001$).

Conclusion: The risk for nocturnal hypoglycemia was lower with glimepiride in combination with morning and bedtime insulin glargine than with glimepiride in combination with bedtime NPH insulin in patients with type 2 diabetes. Morning insulin glargine provided better glycemic control than did bedtime insulin glargine or bedtime NPH insulin.

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For members of the 4001 Study Group, see the Appendix, available at www.annals.org.

Type 2 diabetes is an increasing health problem in all western societies (1); the development of macrovascular complications in patients with type 2 diabetes is a major determinant of morbidity and mortality rates (1, 2). It has also been demonstrated that achieving good glycemic control substantially contributes to the prevention of microvascular complications in patients with type 2 diabetes (3). In addition, epidemiologic association analysis of the data suggests that macrovascular complications can also be prevented (4). However, current therapeutic approaches have not attained the defined targets of good metabolic control in most patients with type 2 diabetes (5).

During the natural course of type 2 diabetes, β-cell function is progressively lost (6), which limits the period when lifestyle modification, diet, and oral antidiabetic drug therapy are sufficient to meet targets of glycemic control. Thus, the therapeutic regimens for patients with type 2 diabetes have to be continually adapted to allow patients to consistently achieve and maintain good glycemic control. Patients with type 2 diabetes benefit from the addition of insulin to their therapeutic regimen (7–9). However, some patients express reservations regarding the administration and side effects of insulin therapy (10); therefore, effective and convenient regimens must be developed. Combination therapy with oral antidiabetic drugs and bedtime neutral protamine Hagedorn (NPH) insulin has proven to be as effective as other, more complex insulin regimens and is associated with less weight gain (11, 12). Combination therapy with insulin and oral antidiabetic drugs is a regimen that can be managed at outpatient visits and that can be conveniently adapted to the patient's needs by adjusting the insulin dose on the basis of self-measured fasting blood glucose levels (13)—a therapeutic target predictive of overall glycemic control (13).

There are, however, limitations to achieving optimal results in daily practice with a combination of oral antidiabetic drugs and NPH insulin. Neutral protamine Hagedorn insulin exhibits a peak in its time–action profile 4 to 6 hours after injection; thus, bedtime NPH insulin is associated with a risk for nocturnal hypoglycemia (14). This risk may limit the feasibility of titrating the NPH insulin dose to reach adequately low fasting blood glucose target values. Furthermore, the activity profile of NPH insulin is too short to provide optimal 24-hour insulin supplementation. Insulin glargine (Lantus, Aventis, Bridgewater, New Jersey) is a recently introduced human insulin analogue that exhibits a 24-hour action profile with no pronounced peak (15–17). One study of patients with type 2 diabetes who were treated with basal and bolus insulin (18) and one study of patients with type 2 diabetes who were receiving oral antidiabetic drugs (14) have suggested that the addition of insulin glargine, injected at bedtime, decreases the risk for nocturnal hypoglycemia compared with NPH insulin. Thus, insulin glargine is an improved basal component for combination regimens with oral antidiabetic drugs in the treatment of type 2 diabetes.

It remains unclear whether insulin glargine provides both better metabolic control and decreases the risk for hypoglycemia than compared with NPH insulin when used with sulfonylureas, such as glimepiride. The best timing for insulin glargine administration is also unclear. We investigated the efficacy and safety of a combination therapy of sulfonylurea (3 mg of glimepiride) with either morning insulin glargine, bedtime insulin glargine, or bedtime NPH insulin in patients with type 2 diabetes whose diabetes was poorly controlled with oral antidiabetic drugs alone.

Context

Insulin glargine is a long-acting insulin preparation that has recently become available. Its optimal role in the treatment of type 2 diabetes is being defined.

Contribution

In this randomized, controlled trial of patients who were taking the sulfonylurea glimepiride, those receiving morning glargine had greater improvement in hemoglobin A_{1c} levels and less frequent nocturnal hypoglycemia than did patients receiving either bedtime neutral protamine Hagedorn (NPH) or bedtime glargine.

Implications

Morning glargine may be a better option for optimizing glycemic control in patients with type 2 diabetes who are also taking sulfonylureas than is either bedtime glargine or bedtime NPH.

–The Editors

METHODS

Study Design

Our study was a 28-week, open-label, randomized, controlled, multinational, multicenter, parallel-group clinical trial. Patients with type 2 diabetes who did not achieve good metabolic control while receiving oral antidiabetic drugs had their oral agents replaced by 3 mg of glimepiride for 4 weeks and were then randomly assigned to receive additional treatment for 24 weeks with insulin glargine in the morning or at bedtime or NPH insulin at bedtime. Our primary objective was to investigate the effect of the different treatment regimens on glycemic control (hemoglobin A_{1c} [HbA_{1c}]) and on the percentage of patients who experienced hypoglycemia. Secondary objectives were to compare the three different interventions in terms of response rates, blood glucose levels, insulin dose, and body weight, as well as adjustment of insulin dose by the investigator. A total of 111 centers in 13 European countries participated in this study. The institutional ethics committee of each participating center approved the trial, and written informed consent was obtained from all participants before enrollment in the study.

Patients

We recruited patients from January 2000 to October 2000; treatment took place between February 2000 and June 2001. Criteria for study inclusion were as follows: 1) type 2 diabetes, 2) age younger than 75 years, 3) body mass index less than 35 kg/m^2, and 4) previous oral therapy with any sulfonylurea as monotherapy or in combination with metformin or acarbose. Furthermore, the fasting blood glucose level had to be 6.7 mmol/L or greater ($\geq$120 mg/dL), and the HbA_{1c} level had to be between 7.5% and 10.5%. Main exclusion criteria were as follows: 1) pregnancy or breast-feeding, 2) pretreatment with insulin or any investigational drugs within the previous 3 months, or 3) presence of any clinically relevant somatic or mental diseases.

Screening Phase

The study consisted of a 4-week screening phase and a 24-week treatment phase. Before the start of the study, patients gave informed consent, medical histories were recorded, physical examinations were performed, and inclusion as well as exclusion criteria were satisfied. Blood samples were taken for determination of HbA_{1c} levels, complete hematologic and clinical chemistry analyses, and lipid status. Patients were trained to use the OptiPen Pro (Aventis, Bridgewater, New Jersey) insulin injection device and the One Touch II (LifeScan, Milpitas, California) blood glucose meter. Patients discontinued use of their previous oral antidiabetic drug treatment and received 3 mg of glimepiride in the morning. Patients provided a complete 8-point, 24-hour blood glucose profile on the 2 consecutive days of the screening phase.

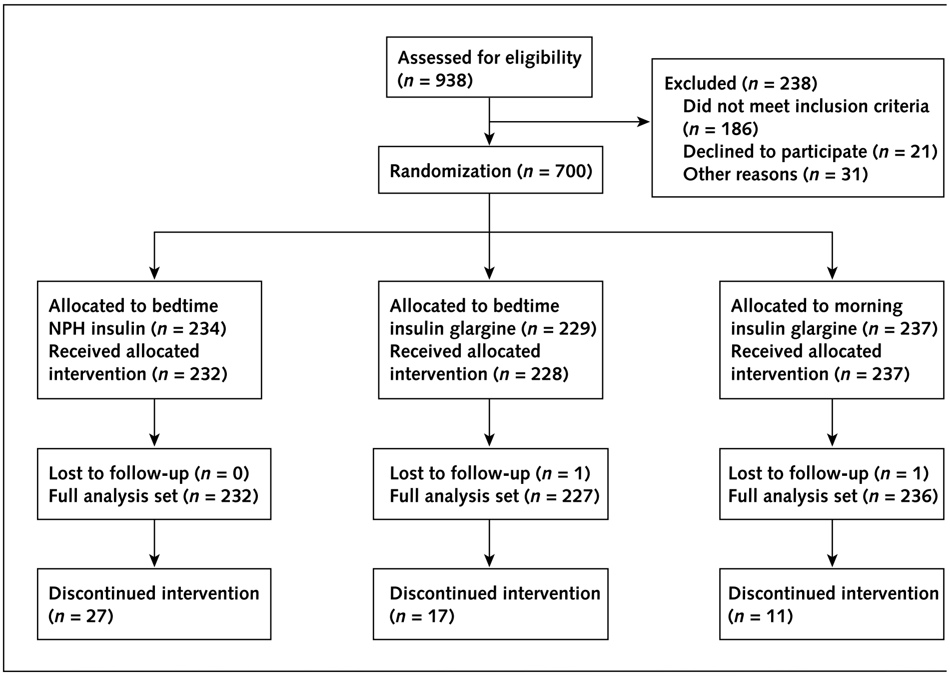
Randomization

A sequence of screening patient numbers was assigned to each study center. All patients who had entered the screening phase received a patient number. With a randomization schedule generated by the sponsor, eligible patients were linked sequentially to treatment codes allocated at random. This schedule was stratified by center on a 1:1:1 basis.

Intervention

During the treatment phase, patients visited the investigation sites 1, 2, 3, 4, 6, 8, 12, 16, 20, and 24 weeks after randomization. At these visits, patients had to provide daily self-measured fasting blood glucose values, and episodes of hypoglycemia were recorded in a standardized diary. The investigators checked these values, and the insulin dose was

Figure 1. **Trial profile.**



NPH = neutral protamine Hagedorn.

adjusted according to a predefined titration regimen. Furthermore, vital signs (including blood pressure and body weight) were recorded at every visit. At baseline, 12 weeks, and 24 weeks after randomization, blood was drawn for measurement of complete hematologic and clinical chemistry analyses. At baseline and 8, 12, and 24 weeks, blood was drawn for measurement of HbA_{1c} levels, and patients had to provide an 8-point daily blood glucose profile on 2 consecutive days.

When combination therapy was initiated, insulin glargine or NPH insulin was injected subcutaneously once daily. The insulin glargine and NPH insulin formulation consisted of a cartridge containing 3 mL of either insulin preparation. Neutral protamine Hagedorn insulin had to be mixed thoroughly by rotating the injection device. The insulin dose for the first day of the treatment phase was calculated according to the formula of Holman and Turner (19) by subtracting 2.8 mmol/L (50 mg/dL) from the actual fasting blood glucose value and dividing the result by 0.56 mmol/L (10 mg/dL). During the treatment phase, the insulin dose was titrated every visit by using a predefined regimen: If the fasting blood glucose level was greater than 5.6, 6.7, 7.8, or 8.9 mmol/L (>100, 120, 140, 160 mg/dL) for at least 1 of 2 consecutive days before the visit with no hypoglycemia, the insulin dose was increased by 2, 4, 6, or 8 units, respectively. Doses of glimepiride remained unchanged throughout the study.

Analytical Methods

Hemoglobin A_{1c} levels were measured by high-performance liquid chromatography (Bio-Rad Diamat, Munich, Germany) in the central laboratory (INTERLAB, Munich, Germany); the reference range was 4.4% to 6.1%. Hematologic and clinical chemistry analyses were measured in local laboratories according to standard laboratory procedures.

Statistical Analysis

The primary efficacy assessment was the change in HbA_{1c} level from baseline to end point and the frequency of patients who experienced hypoglycemic episodes during the study. Secondary efficacy measurements were HbA_{1c} level (≤7.5%), fasting blood glucose levels (≤5.6 mmol/L) [≤100 mg/dL]), response rates, and mean 24-hour blood glucose values. Hypoglycemia was defined as symptomatic or asymptomatic (blood glucose level < 4.2 mmol/L [<75 mg/dL]). Severe hypoglycemia was defined as an event with symptoms consistent with hypoglycemia that required the assistance of another person and that was associated with a blood glucose level less than 2.8 mmol/L (<50 mg/dL) or that was followed by prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. Nocturnal hypoglycemia was defined as hypoglycemia that occurs while the patient is asleep—between bedtime after the evening injection and before the patient awakes in the morning.

An analysis of covariance was performed to compare the changes in HbA_{1c} values; treatment and country were fixed effects, and HbA_{1c} baseline values were covariates. One-sided 95% CIs or two-sided 90% CIs, respectively, were evaluated (equivalent to an α level of 0.05) on an intention-to-treat basis (full-analysis set). Because the country in which the study was conducted was a significant determinant of change in HbA_{1c} level ($P < 0.001$; analysis of covariance), we assessed the homogeneity of treatment differences across countries by evaluating treatment-by-country interaction for the change in HbA_{1c} level. For the secondary efficacy analysis, we performed an analysis of covariance for all continuous secondary variables by using change from baseline to end point; treatment and country were fixed effects, and the corresponding baseline value was a covariate. Categoric secondary variables were analyzed for treatment differences by using Cochran–Mantel–Haenszel tests, stratified by country. P values less than 0.05 were deemed statistically significant. Continuous data are presented by unadjusted and adjusted means and corresponding CIs. Statistical analyses were performed by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

Sample Size Justification

Based on the assumption of a standard deviation of $\sigma = 2.0\%$, a difference of $\Delta = 0.5\%$ for HbA_{1c} reductions among treatment groups can be detected with an α error of 0.05 and a β error of 0.2. This equates to a statistical power of 80% with 199 patients per group. With use of a 1:1:1 randomization, 597 patients would be required for this study. Assuming a nonevaluable rate of 20%, a total of 720 patients (240 patients per group) would need to be enrolled in this study.

Role of the Funding Sources

The study sponsors were involved in the study design, selection of study centers, collection and statistical analysis of the data, and provision of the study material. They reviewed the manuscript, with emphasis on consistency of data and statistical interpretation. The study sponsors had no role in the decision to submit the manuscript for publication.

RESULTS

Patient Characteristics

Seven hundred patients were randomly assigned to the three interventions: 236 received morning insulin glargine, 232 received bedtime NPH insulin, and 227 received bedtime insulin glargine. These 695 patients represent the intention-to-treat sample (full-analysis set) (**Figure 1**). Protocol violations were due to pretreatment with insulin in the 3 months before the study, use of drugs to reduce blood glucose levels other than as specified in the protocol, lack of HbA_{1c} measurement, or the use of systemic corticosteroids. Demographic characteristics at baseline did not significantly differ among the three treatment groups (**Table 1**). Concomitant medication consisted of angiotensin-converting enzyme inhibitors (335 patients [48%]), lipid-lowering drugs (253 patients [36%]), antithrombotic agents (234 patients [34%]), and β-blockers (161 patients [23%]). Therefore, the relevant concomitant diseases primarily affected the cardiovascular system (441 patients [64%]). Patients had diabetic retinopathy (129 patients [19%]), neuropathy (167 patients [24%]), nephropathy (44 patients [6%]), and peripheral macroangiopathy (93 patients [13%]). Before enrollment, the oral antidiabetic drugs predominantly used were sulfonylureas (675 patients [97%]) and metformin (463 patients [67%]).

Insulin Dose

Initial insulin doses were similar in the three treatment groups (**Figure 2**). Over the study duration, the insulin doses increased from a mean (±SD) of 19 ± 11 IU to 40 ± 24 IU with morning insulin glargine, from 19 ± 11 IU to 37 ± 22 IU with bedtime NPH insulin, and from 20 ± 11 IU to 39 ± 21 IU with bedtime insulin glargine. The change of the insulin dose from baseline to end point did not significantly differ among the groups ($P = 0.06$) (**Figure 2**).

Glycemic Control

HbA_{1c}

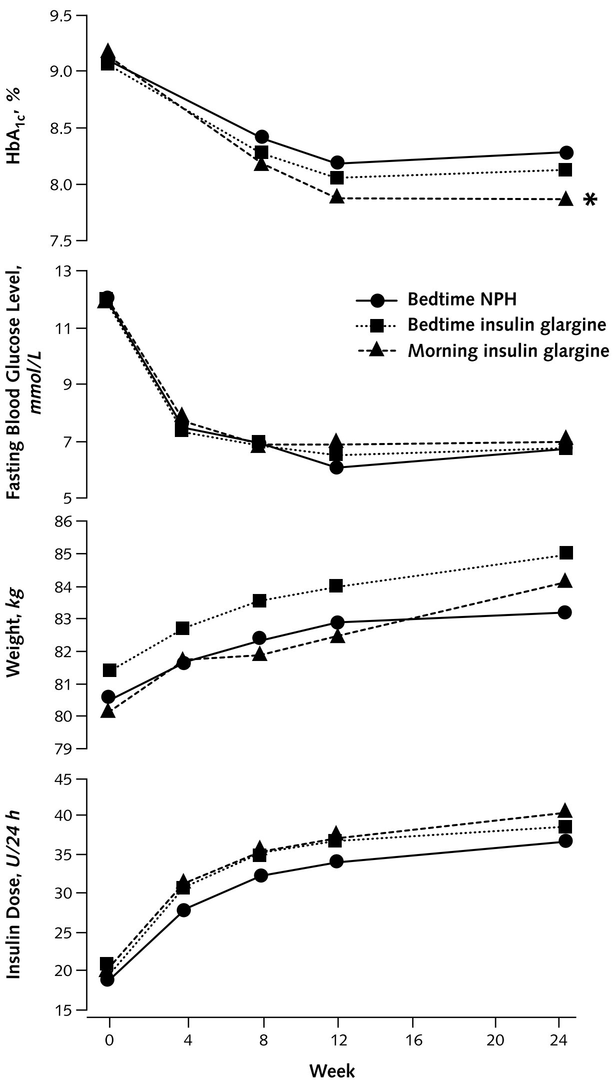
Over the 24-week treatment period, HbA_{1c} levels improved from 9.1% ± 1.0% to 7.8% ± 1.2% with morning insulin glargine, from 9.1% ± 1.1% to 8.3% ± 1.3% with bedtime NPH insulin, and from 9.1% ± 1.0% to 8.1% ± 1.3% with bedtime insulin glargine (**Figure 2**). Hemoglobin A_{1c} levels improved by −1.24% (two-sided 90% CI, −1.10% to −1.38%) with morning insulin

Table 1. **Baseline Characteristics of Patients Treated with Bedtime Neutral Protamine Hagedorn Insulin, Bedtime Insulin Glargine, or Morning Insulin Glargine***

Characteristic	Bedtime NPH Insulin Group	Bedtime Insulin Glargine Group	Morning Insulin Glargine Group	Overall *P* Value
Patients, *n*	232	227	236	
Men/women, *n/n*	119/113	132/95	122/114	>0.2
Age, *y*	62 ± 9	60 ± 9	61 ± 9	0.10
Weight, *kg*	81.0 ± 14.9	82.1 ± 13.6	80.7 ± 15.8	>0.2
BMI, *kg/m²*	28.9 ± 3.9	28.7 ± 3.9	28.6 ± 4.5	>0.2
HbA_{1c} level, %	9.1 ± 1.1	9.1 ± 1.0	9.1 ± 1.0	>0.2
Median duration of diabetes (range), *y*	9.3 (1–39)	8.2 (1–51)	9.0 (0–38)	0.10
Median duration of oral antidiabetic drug treatment (range), *y*	7.6 (0–38)	6.2 (1–30)	7.2 (0–38)	0.04
C-peptide level, *nmol/L*	1.07 ± 0.68	1.04 ± 0.59	0.96 ± 0.66	0.08

* Data expressed with a plus/minus sign are the mean ± SD. BMI = body mass index; HbA_{1c} = hemoglobin A_{1c}; NPH = neutral protamine Hagedorn.

Figure 2. **Hemoglobin A_{1c} (*HbA_{1c}*) values, fasting blood glucose levels, body weight, and mean insulin dose measurements.**



These measures were determined at baseline and over the 24-week treatment period with a combination therapy of glimepiride (3 mg) and either neutral protamine Hagedorn (*NPH*) insulin injected at bedtime, insulin glargine injected at bedtime, or insulin glargine injected in the morning. *Decrease in hemoglobin A_{1c} from baseline: $P < 0.001$ for morning insulin glargine versus bedtime neutral protamine Hagedorn insulin and $P = 0.008$ for morning insulin glargine versus bedtime insulin glargine.

glargine, −0.96% (CI, −0.81% to −1.10%) with bedtime insulin glargine, and −0.84% (CI, −0.69% to −0.98%) with NPH insulin. Improvement in HbA_{1c} was more pronounced with morning insulin glargine than with NPH insulin (0.40% [CI, 0.23% to 0.58%]; $P < 0.001$) and bedtime insulin glargine (0.28% [CI, 0.11% to 0.46%]; $P = 0.008$) (**Table 2**). More patients reached an HbA_{1c} level of 7.5% or less with morning insulin glargine (102 of 236 [43%]) than with bedtime NPH insulin (74 of 232 [32%]; $P = 0.017$) and bedtime insulin glargine (75 of 227 [33%]; $P = 0.021$) (**Table 2**).

Fasting Blood Glucose

Fasting blood glucose levels improved in all three groups: from 12.1 ± 3.0 to 7.0 ± 1.9 mmol/L (218 ± 54 to 126 ± 34 mg/dL) with morning insulin glargine, from 12.2 ± 3.2 to 6.9 ± 1.9 mmol/L (220 ± 58 to 124 ± 34 mg/dL) with bedtime NPH insulin, and from 12.0 ± 2.9 to 6.8 ± 1.9 mmol/L (216 ± 52 to 122 ± 34 mg/dL) with bedtime insulin glargine (**Figure 2**). The average reduction in fasting blood glucose level achieved over the study duration did not differ among the groups (for all groups, $P > 0.2$).

Diurnal Blood Glucose Profiles

At baseline, diurnal blood glucose levels were similar (**Figure 3**) in all three groups. Mean blood glucose level improved in all three groups: from 13.8 ± 3.7 to 8.6 ± 2.1 mmol/L (248 ± 67 to 155 ± 38 mg/dL) with morning insulin glargine, from 13.9 ± 3.9 to 9.7 ± 2.6 mmol/L (250 ± 70 to 174 ± 46 mg/dL) with bedtime NPH insulin, and from 13.8 ± 3.5 to 9.3 ± 2.3 mmol/L (248 ± 62 to 167 ± 42 mg/dL) with bedtime insulin glargine. The morning insulin glargine group showed a greater decrease in mean daily blood glucose levels compared with both the bedtime NPH insulin group ($P <$ 0.001) and the bedtime insulin glargine group ($P =$ 0.002).

Hypoglycemia

The number of patients experiencing episodes of hypoglycemia was similar among all treatment groups (**Table 3**). The number of patients experiencing episodes of nocturnal hypoglycemia was lower with both morning insulin glargine (39 of 236 [17%]) and bedtime insulin glargine (52 of 227 [23%]) than with bedtime NPH insulin (89 of 232 [38%]) ($P < 0.001$). Therefore, the frequency of patients experiencing nocturnal hypoglycemia decreased by 56% in the morning insulin glargine group and by 42% in the bedtime insulin glargine group. In addition, fewer patients experienced symptomatic hypoglycemia with bedtime insulin glargine (98 of 227 [43%]) than with bedtime NPH insulin (135 of 232 [58%]; $P = 0.001$) and morning insulin glargine (133 of 236 [56%]; $P = 0.004$) (**Table 3**). The frequency of severe hypoglycemia calculated per 100 patient-years was 5.5 with morning insulin glargine, 12.2 with bedtime NPH insulin, and 3.8 with bedtime insulin glargine.

Adverse Events

The number of adverse events during the treatment phase was similar in all three treatment groups (bedtime insulin glargine, 414; bedtime NPH insulin, 423; and

Table 2. **Effect of Bedtime Neutral Protamine Hagedorn Insulin, Bedtime Insulin Glargine, or Morning Insulin Glargine on Glycemic Control***

Variable	Bedtime NPH Insulin Group	Bedtime Insulin Glargine Group	Morning Insulin Glargine Group	Overall *P* Value
Patients, *n*	232	227	236	
Mean improvement in HbA_{1c} level† (90% CI), %	−0.84 (−0.69 to −0.98)	−0.96‡ (−0.81 to −1.10)	−1.24§ (−1.10 to −1.38)	<0.001
HbA_{1c} level < 7.5%, *n* (%)	74 (32.5)	75 (33.6)‖	102 (43.4)¶	0.022

* HbA_{1c} = hemoglobin A_{1c}; NPH = neutral protamine Hagedorn.
† From end point to baseline.
‡ $P > 0.2$ versus bedtime NPH insulin.
§ $P = 0.008$ versus bedtime glargine and $P = 0.0002$ versus bedtime NPH insulin.
‖ $P > 0.2$ versus bedtime NPH insulin.
¶ $P = 0.021$ versus bedtime glargine and $P = 0.017$ versus bedtime NPH insulin.

morning insulin glargine, 403). A possible relationship to the study medication was suggested for 45 adverse events with morning insulin glargine, 55 adverse events with bedtime NPH insulin, and 36 adverse events with bedtime insulin glargine. Three patients died during the study: two in the bedtime insulin glargine group and one in the bedtime NPH insulin group. No deaths were related to the study medication. Withdrawals due to adverse events were rare and similar in the treatment groups (morning insulin glargine, 5 of 236 patients [2.1%]; bedtime NPH insulin, 7 of 232 patients [3.0%]; and bedtime insulin glargine, 4 of 227 patients [1.8%]).

Body Weight

Weight gain during the treatment period was 3.9 ± 4.5 kg with morning insulin glargine, 2.9 ± 4.3 kg with bedtime NPH insulin, and 3.7 ± 3.6 kg with bedtime insulin glargine. The weight gain did not significantly differ among the treatment groups ($P > 0.2$).

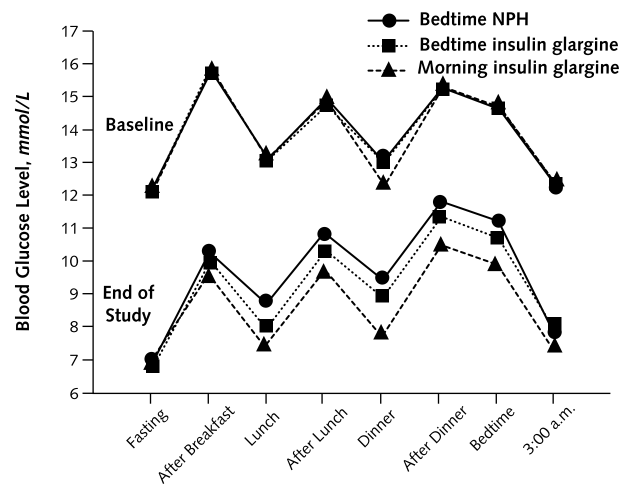
DISCUSSION

Combination therapy with oral antidiabetic drugs during the day and an intermediate-acting NPH insulin given at bedtime has proven to be an effective and feasible therapeutic approach in patients with type 2 diabetes (7). Because of the linear correlation between fasting blood glucose and HbA_{1c} levels, the insulin dose has to be titrated to a fasting blood glucose level of 5.56 mmol/L or less (≤100 mg/dL) to achieve good metabolic control (HbA_{1c} level ≤ 7.5%) (13). However, aggressive titration to target is associated with a risk for nocturnal hypoglycemia; this is especially true with NPH insulin because its peak activity occurs approximately 5 hours after injection (7, 20). Since insulin glargine is known to have an action profile with no pronounced peak and a duration of action of approximately 24 hours (15, 16), we compared the safety and efficacy of a combination therapy with sulfonylurea and bedtime NPH insulin with insulin glargine given either in the morning or at bedtime.

Insulin glargine injected in the morning resulted in better glycemic control than did bedtime NPH insulin. This can be explained by the longer action profile of insulin glargine and, therefore, better 24-hour glycemic control (15, 16). In accordance with this time–action profile, the self-monitored diurnal blood glucose profiles of the patients showed that, with the exception of fasting blood glucose, blood glucose levels were lower during the entire day in the morning insulin glargine group than in the bedtime NPH insulin group. This clinically confirms that the duration of action of insulin glargine is 24 hours because the blood glucose lowering effect persists until the next day's injection.

The finding that insulin glargine results in better glycemic control only when given in the morning was unexpected and is not easy to explain. Previous studies comparing basal insulin therapy with bedtime NPH insulin versus morning NPH insulin have not demonstrated better glycemic control with NPH insulin injected in the morning.

Figure 3. **Diurnal blood glucose profile.**



Diurnal blood glucose levels were measured at baseline (0 weeks) and before the last visit (24 weeks) in patients who received bedtime neutral protamine Hagedorn (*NPH*) insulin, bedtime insulin glargine, or morning insulin glargine. Profiles at baseline did not differ significantly. *P* values indicate overall differences among treatment groups in the decrease of blood glucose values from baseline. Fasting, $P > 0.2$; after breakfast, $P = 0.01$; lunch, $P < 0.001$; after lunch, $P < 0.001$; dinner, $P < 0.001$; after dinner, $P < 0.001$; bedtime, $P < 0.001$; and 3:00 a.m., $P = 0.04$.

Table 3. **Patients with Hypoglycemic Episodes Treated with Bedtime Neutral Protamine Hagedorn Insulin, Bedtime Insulin Glargine, or Morning Insulin Glargine***

Variable	Bedtime NPH Insulin Group	Bedtime Insulin Glargine Group	Morning Insulin Glargine Group	Overall *P* Value
Patients, *n*	232	227	236	
All episodes of hypoglycemia, *n (%)*	173 (75)	155 (68)	175 (74)	>0.2
All episodes of symptomatic hypoglycemia, *n (%)*	135 (58)	98† (43)	133 (56)	0.002
Nocturnal hypoglycemia, *n (%)*	89 (38)	52‡ (23)	39‡ (17)	<0.001
Severe hypoglycemia, *n (%)*	6 (2.6)	4 (1.8)	5 (2.1)	>0.2

* NPH = neutral protamine Hagedorn.
† $P = 0.004$ versus morning insulin glargine and $P = 0.001$ versus bedtime NPH insulin.
‡ $P < 0.001$ versus bedtime NPH insulin.

On the contrary, some studies have demonstrated better glycemic control with bedtime NPH insulin (21–24). One could speculate that the reason for the better glycemic control with morning insulin glargine is that the glucose-lowering effect of insulin glargine given in the morning together with glimepiride might be higher during the first 12 hours after insulin glargine injection. However, as glimepiride was the only oral glucose-lowering agent used in this study, no conclusions can be made about the efficacy of the oral antidiabetic treatment in this study and the potential benefits of using other oral hypoglycemic agents in combination with insulin. A future study could compare insulin glargine administered in the morning and evening in combination with metformin.

Alternatively, the differences could result from lack of adherence to the titration regimen. Physicians and patients might be more afraid of nocturnal hypoglycemia with bedtime insulin administration than with morning administration. It seems that the fear of nocturnal hypoglycemia may prevent adherence to insulin therapy and thus prevent good glycemic control (25); the result is a decrease in quality of life in the long term for patients with type 2 diabetes (26).

The results of our study confirm earlier reports (14, 18) that insulin glargine is associated with fewer episodes of nocturnal hypoglycemia than is NPH insulin. Of note, incidence of nocturnal hypoglycemia was lower with both morning and bedtime insulin glargine than with bedtime NPH insulin (**Table 2**). Because the overall rate of blood glucose levels less than 4.2 mmol/L (<75 mg/dL) was the same in all treatment groups (**Table 3**), the lower incidence of nocturnal hypoglycemia comes at the expense of increased numbers of blood glucose levels less than 4.2 mmol/L (<75 mg/dL) during the rest of the day. Also of importance is the rate of severe hypoglycemia, which was lowest with insulin glargine and similar to the rate observed in patients with type 2 diabetes who were treated with insulin in the U.K. Prospective Diabetes Study (2.3 events per 100 patient-years), Veterans Cooperative Study (3.0 events per 100 patient-years), and Veterans Implantable Insulin Pumps Study (7.83 events per 100 patient-years) (20). In our study, a similar frequency of hypoglycemia and glycemic control was achieved by using the less complicated insulin glargine once-daily regimen.

In our study, the use of a predefined titration regimen to achieve a fasting blood glucose level of 5.56 mmol/L or less (≤100 mg/dL) was based on an earlier study showing that such a target was required to achieve an HbA_{1c} level less than 7.5% (13). Although the target fasting blood glucose of 5.56 mmol/L or less (≤100 mg/dL) was attained in only a minority of patients (approximately 25%), two thirds of the patients attained fasting blood glucose less than 7 mmol/L (<126 mg/dL). Therefore, more aggressive titration (to a fasting blood glucose target ≤ 5.56 mmol/L [≤100 mg/dL]) than that achieved in this multinational, multicenter trial is needed.

In conclusion, a simplified combination regimen with one injection of insulin glargine, one oral agent, and one self-monitored blood glucose measurement per day has been proven to be effective and well tolerated in patients with type 2 diabetes; flexibility and timing of insulin administration are additional benefits. In terms of both glycemic control and avoidance of nocturnal hypoglycemia, insulin glargine provides a superior basal insulin supply compared with bedtime NPH insulin. To our knowledge, this is the first study using a prebreakfast injection of insulin glargine. Therefore, further studies may be needed to confirm the findings in this study.

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Appendix: The HOE 901/4001 Study Group

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