Original Article

ONCE-DAILY INSULIN GLARGINE COMPARED WITH TWICE-DAILY NPH INSULIN IN PATIENTS WITH TYPE 1 DIABETES

Kenneth S. Hershon, MD, FACE, FACP,[1] Thomas C. Blevins, MD, FACE,[2] Christy A. Mayo, MPH,[3] and Ralf Rosskamp, MD[4]

ABSTRACT

Objective: To present the findings in a randomized, parallel-group study, comparing once-daily insulin glargine with twice-daily NPH insulin in patients with type 1 diabetes previously treated with multiple daily injections of basal and regular insulin.

Methods: Of 394 patients with type 1 diabetes treated for up to 28 weeks, 195 received insulin glargine and 199 received NPH insulin, in addition to preprandial regular insulin. Glycemic control and hypoglycemic episodes were assessed.

Results: A greater mean decrease in fasting blood glucose (FBG) was achieved at endpoint with insulin glargine than with NPH insulin (−21 mg/dL versus −10 mg/dL [−1.17 mmol/L versus −0.56 mmol/L]; $P = 0.015$), and a greater percentage of patients treated with insulin glargine reached the target FBG (32.6% versus 21.3%; $P = 0.015$). Similar percentages of patients in both treatment groups achieved glycosylated hemoglobin values of 7.0% or less at endpoint (insulin glargine, 35.8%; NPH insulin, 35.4%). After the 1-month titration phase, the percentage of patients who reported at least one symptomatic hypoglycemic event confirmed by a blood glucose value of less than 50 mg/dL (2.8 mmol/L) was significantly lower with insulin glargine than with NPH insulin (73.3% versus 81.7%; $P = 0.021$). Furthermore, the percentage of patients who reported at least one symptomatic hypoglycemic event confirmed by a blood glucose value of less than 36 mg/dL (2.0 mmol/L) was significantly lower with insulin glargine than with NPH insulin (36.6% versus 46.2%; $P = 0.033$).

Conclusion: Once-daily insulin glargine was at least as effective as twice-daily NPH insulin in improving fasting glycemic control and resulted in fewer reported symptomatic hypoglycemic events. **(Endocr Pract. 2004;10: 10-17)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **ADA** = American Diabetes Association; **FBG** = fasting blood glucose; **HbA1c** = glycosylated hemoglobin; **SD** = standard deviation; **SE** = standard error

INTRODUCTION

In patients with diabetes, good glycemic control has been shown to prevent or delay microvascular complications (1,2). Several studies have demonstrated that decreasing glycosylated hemoglobin (HbA1c) levels to 7.0% (normal, 2.8 to 6.0%) and maintaining them at that level—or lower, if possible—reduces complications and mortality in patients with type 1 and type 2 diabetes (1-5). Although management should be individualized to meet each patient's needs, general guidelines such as those provided by the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) should be consulted when determining each patient's treatment goals. Specifically, ADA has established an HbA1c goal of less than 7.0% and suggests that additional action, such as diet, exercise, insulin, or orally administered agents, should be taken when HbA1c exceeds 8.0% (6). Furthermore, AACE has defined an HbA1c goal of less than 6.5% and recommends performance of a glycemic assessment at least twice a year in patients who are at target HbA1c and quarterly or more frequently for patients who are above target HbA1c or are undergoing a change in therapy (7). These metabolic guidelines help to provide many benefits by preventing or delaying microvascular complications; however, they can also contribute to a greater risk of increased frequency of hypoglycemia (8).

Although the number and types of therapeutic modalities for diabetes have grown in recent years, insulin is the only available treatment for type 1 diabetes. Despite medical advances, including the relatively recent introduction

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From the [1]North Shore Diabetes and Endocrine Associate, New Hyde Park, New York, [2]Center for Clinical Research, Austin, Texas, [3]Quintiles, Inc., Kansas City, Missouri, and [4]Aventis Pharmaceuticals Inc., Bridgewater, New Jersey.
Address correspondence and reprint requests to Dr. K. S. Hershon, North Shore Diabetes and Endocrine Associate, 3003 New Hyde Park Road, Suite 201, New Hyde Park, NY 11042.

of short-acting insulin analogues, patients and physicians remain concerned about the risk of hypoglycemic episodes for patients treated with insulin. Hypoglycemia is the most common adverse event of intensive diabetes management (9) and is incriminated in approximately 4% of deaths among patients with type 1 diabetes (10). Therefore, hypoglycemia can be considered the major limiting factor in achieving glycemic goals. Thus, a need exists for insulins with pharmacologic profiles that offer a lower risk of hypoglycemia.

Choosing a long-acting basal insulin has been difficult because traditionally available preparations may exert unpredictable blood glucose-lowering effects (11,12). Insulin glargine (Lantus), a human insulin analogue produced by recombinant DNA technology, provides a constant, smooth basal level of insulin for a 24-hour period after a single daily injection (13). Because of the changes in the primary amino acid sequence, insulin glargine is soluble in an acidic preparation before injection, but it forms a precipitate when it enters the neutral pH environment after subcutaneous injection. The precipitate forms a reservoir from which the drug is slowly absorbed. Investigators have shown that a seventh phenol specifically bound to the hexamer of crystalline insulin glargine increases the interhexamer forces (14). In addition, several other interhexamer interactions that stabilize insulin glargine crystals have been identified (15). This stabilization provides a means for the desired protraction of the hypoglycemic effect of insulin glargine.

In a multicenter, randomized, open-label, parallel-group study comparing once-daily bedtime insulin glargine with once- or twice-daily NPH human insulin in patients with type 1 diabetes previously treated with insulin, both treatments were equally effective in improving and maintaining glycemic control (16). In comparison with patients treated with NPH insulin, however, a lower percentage of patients treated with insulin glargine experienced symptomatic, nocturnal, or severe hypoglycemia, confirmed by a blood glucose level of less than 36 mg/dL (2.0 mmol/L). Because most patients with type 1 diabetes use NPH insulin twice daily, we conducted a subgroup analysis of that study by using only data from patients treated with once-daily insulin glargine and twice-daily NPH insulin. The purpose of this subgroup analysis was to compare the effect of a once-daily regimen of insulin glargine with a twice-daily regimen of NPH insulin on both the control of blood glucose levels and the number of patients reporting hypoglycemic episodes.

PATIENTS AND METHODS

Study Subjects

The study population consisted of a subset of 394 patients from 48 medical centers (see Appendix) of a total population of 534 men and women, 18 to 80 years of age, with type 1 diabetes. Patients with HbA1c levels of 12.0% or less and postprandial C-peptide values of 1.5 ng/mL (0.5 nmol/L) or less, measured at the screening visit, were eligible for randomization. Exclusion criteria included substantial hepatic or renal impairment, treatment with an orally administered antidiabetic drug within 3 months before study entry, pregnancy, and employment that involved a night shift. In this subgroup analysis, only those patients who had received multiple daily injections of basal and regular insulin for more than 1 year before randomization and who were randomized to once-daily insulin glargine or twice-daily NPH insulin were included. The study protocol was approved by the responsible institutional review boards, and written consents were obtained from all study subjects before enrollment.

Study Design

Detailed information about the design and methods of this study are reported elsewhere (16). Briefly, this report describes results for a subset of patients included in a 28-week, randomized, open-label, parallel-group study comparing the effects of once-daily insulin glargine (Lantus, supplied by Aventis Pharmaceuticals Inc., Bridgewater, NJ) with twice-daily NPH human insulin (NPH human insulin, supplied by Eli Lilly & Co., Indianapolis, IN) on glycemic control and the incidence of hypoglycemia when used as part of a basal-bolus insulin regimen (16). Because insulin glargine is a clear solution and NPH insulin is a cloudy suspension, it was not possible to blind the treatment from patients and investigators. All study participants were instructed not to mix their new insulin.

After a screening phase (1 to 4 weeks), during which patients continued their previous NPH insulin and regular human insulin regimen, study subjects were randomized to receive subcutaneous injections of insulin glargine once daily (bedtime) or NPH insulin twice daily (morning and bedtime). During the 28-week treatment phase, doses of insulin glargine and NPH insulin were titrated by investigators as required to maintain or reach a target premeal (that is, fasting) blood glucose (FBG) concentration of 80 to 120 mg/dL (4.44 to 6.66 mmol/L). If FBG levels exceeded 120 mg/dL (6.66 mmol/L) and no nocturnal symptomatic hypoglycemia was reported, the insulin glargine or NPH insulin dose was increased. If FBG levels were less than 80 mg/dL (4.44 mmol/L) and nocturnal symptomatic hypoglycemia had been reported, then the basal insulin dose was decreased. Regular insulin was administered approximately 30 minutes before meals, and the dose was adjusted to reach and maintain a premeal FBG level of 100 to 120 mg/dL (5.55 to 6.66 mmol/L) and a bedtime level of 100 to 144 mg/dL (5.55 to 8.0 mmol/L).

The treatment phase included eight visits: screening (1 to 4 weeks before randomization); randomization (week 0); and weeks 1, 4, 8, 12, 20, and 28. Study subjects used the One Touch Profile System (Lifescan; Johnson & Johnson, Milpitas, CA) to measure capillary FBG levels at home on 7 consecutive days preceding the baseline visit and at weeks 8, 20, and 28 (or early withdrawal). HbA1c levels were measured at the Diabetes Diagnostic

Laboratory (University of Missouri, Columbia, MO) at baseline and at weeks 8, 20, and 28 (or early withdrawal).

Efficacy and Safety Measures

For the purposes of this report, the primary efficacy measure was the percentage of patients who reported a symptomatic, nocturnal symptomatic, or severe symptomatic hypoglycemic episode during the interval after the 1-month dose titration period and the last day of treatment. Hypoglycemia was not reported as an adverse event unless it fulfilled the criteria for a serious adverse event, which subsequently could be related to the study medication. *Hypoglycemia* was defined by the patient's symptoms and confirmed by a blood glucose level of less than 50 mg/dL (2.8 mmol/L). *Severe hypoglycemia* was defined as any hypoglycemic episode for which the patient required the assistance of another person and was accompanied by a blood glucose level of less than 36 mg/dL (2.0 mmol/L) or was associated with prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. *Nocturnal hypoglycemia* was defined as any hypoglycemic episode that occurred after the patient had his or her evening basal insulin injection and before the morning determination of FBG and morning injection of basal insulin (if applicable). Additional efficacy measures included mean changes in HbA1c and FBG between baseline and endpoint. Safety assessments included adverse event reports and changes in results of clinical chemistry or clinical hematology studies, vital signs, and electrocardiographic findings.

Statistical Analysis

The study protocol was designed with 90% power to detect an average difference of 0.5% in HbA1c between treatment groups at the 0.05 level of significance. A more detailed description of the statistical methods used in the clinical trial is reported elsewhere (16). Analyses of change from baseline to endpoint in HbA1c and FBG were conducted by using analysis of covariance models with parameters for treatment and investigative site and a covariate of baseline HbA1c or FBG. Analyses comparing the percentage of patients with hypoglycemic episodes and the percentages of study subjects who reached target HbA1c and FBG levels between treatments were performed with use of the Cochran-Mantel-Haenszel test. Baseline was defined as the last measurement available before the start of study treatment, and endpoint was defined as the last measurement available during the treatment period.

RESULTS

Demographics

Of the 394 study subjects, 195 received insulin glargine and 199 received human NPH insulin. No statistically significant differences were noted between treatment groups with regard to demographic data and history of diabetes at baseline (Table 1). Mean HbA1c levels ± standard deviation (SD) at baseline were similar in the insulin glargine group and the NPH insulin group (7.7 ± 1.2% versus 7.7 ± 1.1%, respectively). Mean FBG (± SD) at baseline was slightly lower in the insulin glargine group (160 ± 45 mg/dL [8.9 ± 2.5 mmol/L]) than in the NPH insulin group (175 ± 52 mg/dL [9.7 ± 2.9 mmol/L]) (P = 0.021).

A total of 40 patients prematurely withdrew from the study: 24 in the insulin glargine group and 16 in the NPH insulin group. Six patients in the insulin glargine group and one in the NPH insulin group discontinued use of the study medication because of an adverse event. Of these, in only three patients—all in the insulin glargine group—did the investigators consider the adverse events possibly related to the study medication. Adverse events thought not to be associated with the study medication were reported by three patients in the insulin glargine group and one in the NPH insulin group. Statistical analyses were performed on the intention-to-treat population, which constituted all study subjects who were randomized and treated and who had a pretreatment and on-treatment value.

Hypoglycemic Episodes

After the 1-month titration phase, a lower percentage of patients reported at least one episode of symptomatic hypoglycemia confirmed by a blood glucose value of less than 50 mg/dL (2.8 mmol/L) in the insulin glargine group than in the NPH insulin group (73.3% versus 81.7%; P = 0.021) (Fig. 1). Furthermore, the percentage of patients who reported at least one episode of symptomatic hypoglycemia confirmed by a lower blood glucose value of less than 36 mg/dL (2.0 mmol/L) was significantly less with insulin glargine than with NPH insulin (36.6% versus 46.2%; P = 0.033). Likewise, a lower percentage of study subjects in the insulin glargine group reported at least one severe hypoglycemic event confirmed by a blood glucose value of less than 36 mg/dL (2.0 mmol/L) than in the NPH insulin group (2.6% versus 5.1%); however, the difference was not statistically significant. The percentages of patients who reported at least one episode of unconfirmed, symptomatic nocturnal hypoglycemia were similar for both treatment groups (71.2% for the insulin glargine group and 69.5% for the NPH insulin group; P = 0.771).

Glycemic Control

Both insulin glargine and NPH insulin had similar effects on glycemic control. At endpoint, similar reductions from baseline HbA1c (adjusted mean ± standard error [SE]) were achieved in the insulin glargine group and the NPH insulin group (−0.09 ± 0.07% versus −0.19 ± 0.07%, respectively). The percentage of patients at endpoint reaching HbA1c values of 7.0% or less was similar in both groups (35.8% for insulin glargine and 35.4% for NPH insulin). In contrast, the percentage of patients at endpoint achieving HbA1c values of 8.0% or less was slightly higher in the NPH insulin group than in the insulin

Table 1
Demographic Data and Disease Characteristics at Baseline, for Overall Study Group and Stratified by Treatment

Factor	Insulin glargine	NPH human insulin	Total
No. of patients	195	199	394
Sex			
Male	98 (50.3%)	97 (48.7%)	195 (49.5%)
Female	97 (49.7%)	102 (51.3%)	199 (50.5%)
Age (yr)*	37.9 ± 12.6	37.8 ± 11.4	37.8 ± 12.0
Body mass index (kg/m^2)*	25.6 ± 4.2	26.1 ± 4.8	25.9 ± 4.5
Race			
White	185 (94.9%)	192 (96.5%)	377 (95.7%)
African American	8 (4.1%)	3 (1.5%)	11 (2.8%)
Asian/Oriental	…	4 (2%)	4 (1%)
Multiracial	2 (1%)	…	2 (0.5%)
Hispanic ethnicity	6 (3.1%)	7 (3.5%)	13 (3.3%)
Diabetes history*			
Duration of diabetes (yr)	18.2 ± 11.5	16.7 ± 9.5	17.4 ± 10.6
Age at onset (yr)	20.0 ± 11.9	21.4 ± 12.4	20.7 ± 12.2
Duration of insulin treatment (yr)	18.0 ± 11.6	16.4 ± 9.6	17.2 ± 10.6
Metabolic control at baseline			
No. of patients†	190	192	382
Glycosylated hemoglobin (%)*	7.7 ± 1.2	7.7 ± 1.1	7.7 ± 1.2
No. of patients†	178	188	366
Fasting blood glucose*			
mg/dL	160.3 ± 45.0	174.7 ± 52.2	167.5 ± 50.4
mmol/L	8.9 ± 2.5	9.7 ± 2.9	9.3 ± 2.8

*Data are shown as means ± standard deviation.
†The number of subjects is less than the total population because data were missing or not collected from some subjects.

glargine group (74.0% versus 68.9%, respectively). The decrease in FBG level (adjusted mean ± SE) with insulin glargine, however, was significantly greater than with NPH insulin at endpoint (−21 ± 4 mg/dL [−1.17 ± 0.22 mmol/L] versus −10 ± 3 mg/dL [−0.56 ± 0.17 mmol/L], respectively; $P = 0.015$). In addition, a greater percentage of study subjects reached a target FBG level of less than 120 mg/dL (6.66 mmol/L) at endpoint in the insulin glargine group in comparison with the NPH insulin group (32.6% versus 21.3%; $P = 0.015$) (Fig. 2).

Insulin Dose

For achievement of a target FBG level of 80 to 120 mg/dL (4.44 to 6.66 mmol/L), insulin doses were adjusted as appropriate for each study subject. Throughout the study, the mean total daily basal insulin dose was lower in the patients receiving insulin glargine than in those receiving NPH insulin. The mean change in daily basal insulin dose from baseline to endpoint in the insulin glargine group was −7.1 IU, whereas the mean change from baseline to endpoint in the NPH insulin group was +2.3 IU (Fig. 3). For regular human insulin, the mean (± SD) total daily dose for patients receiving insulin glargine increased by 6.1 IU from baseline (17.2 ± 9.8 IU to 23.3 ± 12.7 IU), whereas for patients receiving NPH insulin, the mean total daily dose increased by 1.0 IU from baseline (19.0 ± 11.1 IU to 20.0 ± 12.1 IU). In comparison with baseline values, patients in the insulin glargine group required less insulin at endpoint (−0.6 IU/day), and patients in the NPH group required more insulin at endpoint (+3.3 IU/day).

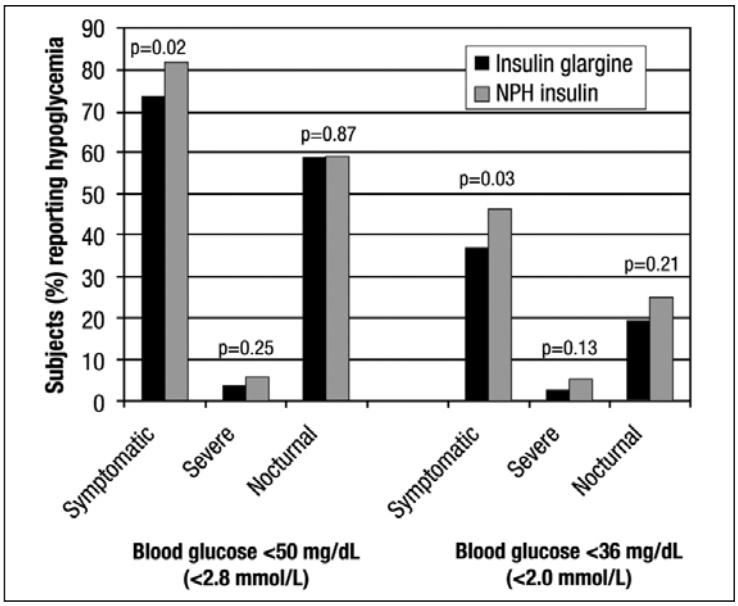

Fig. 1. Percentages of study subjects with at least one episode of hypoglycemia (symptomatic, severe, or nocturnal) during month 2 to endpoint with use of once-daily insulin glargine or twice-daily NPH human insulin.

Safety

Both insulin glargine and NPH insulin were well tolerated; the incidence and spectrum of adverse events were similar in both treatment groups. In both groups, the percentage of patients who experienced at least one treatment-related adverse event was similar (84.6% for insulin glargine and 85.9% for NPH insulin). Similar percentages of subjects in both groups experienced at least one serious adverse event (13.8% for insulin glargine and 13.1% for NPH insulin). Both groups had a small increase in mean weight. In the insulin glargine group, the mean body weight increased from 75.5 ± 14.2 kg at baseline to 76.0 ± 14.5 kg at endpoint. Similarly, the mean body weight increased from 75.0 ± 14.6 kg at baseline to 75.9 ± 15.2 kg at endpoint in the NPH insulin group. The between-treatment weight difference (mean ± SD) for insulin glargine and NPH insulin was not statistically significant (0.7 ± 3.3 kg versus 1.0 ± 2.9 kg, respectively; $P = 0.33$). Insulin glargine-treated subjects reported a slightly higher incidence of injection site pain in comparison with the NPH insulin group (3.6% versus 0.5%, respectively); however, these episodes were mild and did not result in discontinuation of the study medication.

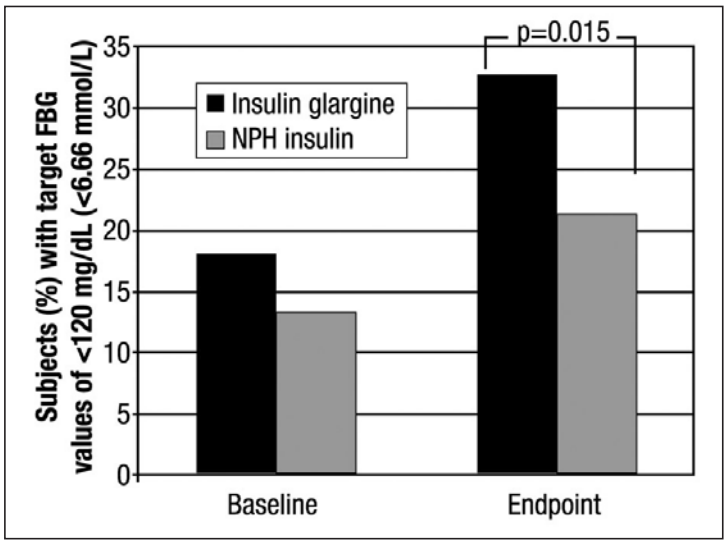

Fig. 2. Percentages of study subjects in the two treatment groups reaching target fasting blood glucose (*FBG*) at baseline and endpoint of the study.

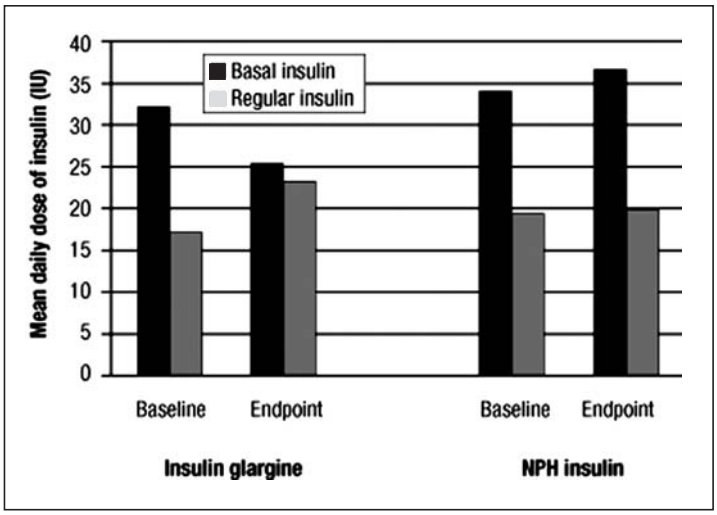

Fig. 3. Mean daily dose of basal and regular insulin at baseline and endpoint of the study for insulin glargine and NPH insulin treatment arms.

DISCUSSION

The results of this subgroup analysis of a 28-week, randomized, open-label study are consistent with the results of other studies that have compared once-daily insulin glargine with twice-daily NPH insulin in terms of glycemic control and symptomatic hypoglycemia (17-21). Moreover, the results of this subanalysis confirm the findings from the analyses in the overall group (16). This study, which compared patients treated with bedtime insulin glargine with patients who received morning and bedtime NPH insulin, suggests that patients treated with insulin glargine may be at lower risk for symptomatic hypoglycemia in comparison with those receiving NPH human insulin twice daily. The NPH insulin group may have been at a slightly higher risk of overall hypoglycemia compared with the insulin glargine group because of the higher total insulin dose. Nevertheless, the total NPH insulin dose was divided, and patients generally received a lower percentage of their total NPH dosage at night; therefore, patients in the NPH insulin group may have been at a lower risk of nocturnal hypoglycemia than were insulin glargine-treated study subjects. No statistically significant differences were found between the two treatment groups relative to the number of patients who reported symptomatic nocturnal hypoglycemia. Overall, insulin glargine-treated patients experienced fewer episodes of nocturnal hypoglycemia in both analyses.

The suggested trend toward a lower incidence of symptomatic nocturnal hypoglycemia in the insulin glargine group could be attributed to the prolonged duration of action of insulin glargine that provides a constant release of insulin with no pronounced peaks in activity. This pattern is in contrast to the intermediate-acting profile of NPH insulin, which peaks in activity 4 to 6 hours after administration (11). Other studies have also shown that patients treated with insulin glargine may be at a lower risk for experiencing nocturnal hypoglycemia (20,21). Although no significant between-treatment differences were noted in the incidence of symptomatic hypoglycemia in either of the study analyses, it would be reasonable to speculate that, had the incidence of absolute hypoglycemia been measured (to capture episodes of asymptomatic hypoglycemia), a significant difference in favor of insulin glargine—such as those demonstrated in similar studies (20,21)—may have been apparent.

Previous studies have shown that once-daily insulin glargine was at least as effective as once- or twice-daily NPH human insulin in achieving glycemic control (20-22). The current analysis further suggests that once-daily insulin glargine is as effective as twice-daily NPH human insulin in lowering HbA1c closer to recommended target levels (7.0% or less) and more effective in lowering FBG levels. Collectively, these data support the findings of the overall analyses.

In the insulin glargine group, the basal insulin dose decreased by approximately −7 IU/day, whereas the bolus regular insulin dose increased by approximately 6 IU/day. These results were similar to the original analyses, in which the basal insulin dose decreased by a mean of −5 IU overall in the insulin glargine group. The need for less basal insulin and the presence of a lower FBG level may allow more aggressive therapy with bolus (fast-acting) insulin in the future. This approach may result in improved FBG with insulin glargine as well as better postprandial control in clinical practice. In future trials, patients with type 1 diabetes should be more aggressively treated to help attain optimal glycemic control and 2-hour postprandial glucose levels, and FBG levels should be monitored.

In the original analyses, the NPH insulin group had an overall increase in both basal and bolus insulin doses of approximately 4 IU. In these analyses, however, little change was noted in basal or bolus insulin dose. HbA1c values improved more with NPH insulin than with insulin

glargine. In light of the greater improvement in FBG levels in the insulin glargine group, one might have expected a better improvement in HbA1c levels; however, perhaps postprandial glucose levels, which were not treated aggressively, limited the improvements in HbA1c. Of note, baseline HbA1c levels were already reasonably well controlled in both groups. This factor may have limited improvements in HbA1c, inasmuch as incremental decreases in HbA1c become increasingly difficult to achieve with low initial HbA1c levels. The trend toward a lower incidence of hypoglycemia in the insulin glargine group suggests that dosing could have been more aggressive without increasing the risk of hypoglycemia. Therefore, it would be reasonable to speculate that had a more aggressive treat-to-target regimen been used in this study, any between-treatment differences in favor of insulin glargine would have been more apparent.

CONCLUSION

In summary, this subgroup analysis supports the results of the full original analyses and suggests that once-daily bedtime insulin glargine is at least as effective as twice-daily NPH insulin in improving fasting glycemic control and may be associated with fewer episodes of symptomatic hypoglycemia in patients with type 1 diabetes. Furthermore, the between-treatment trends in favor of insulin glargine observed in this study suggest that this basal insulin may be well suited to more aggressive treat-to-target regimens.

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APPENDIX

The following list of investigators had patients who fulfilled the criteria for inclusion in the subgroup analysis: Carlos Abraira, MD; David S. H. Bell, MD; Richard W. Bergstrom, MD; Thomas C. Blevins, MD; Nancy J. V. Bohannon, MD; John B. Buse, MD, PhD; Charles Clark, MD; George E. Dailey III, MD; Paresh Dandona, MD; Diana G. Dills, MD; Elliott Eisenbud, MD; Mark N. Feinglos, MD; Raymond I. Fink, MD; Lisa H. Fish, MD; Vivian A. Fonseca, MD; Om P. Ganda, MD; Satish Garg, MD; Ronald Goldberg, MD; Barry J. Goldstein, MD, PhD; Richard A. Guthrie, MD; Kenneth S. Hershon, MD; Irl B. Hirsch, MD; Lois G. Jovanovic, MD; David Kelly, MD; David Klachko, MD; Leslie J. Klaff, MD, PhD; Thomas Littlejohn III, MD; John Malone, MD; Ronald Mayfield, MD; Janet B. McGill, MD; James L. Neifing, MD; Leann Olansky, MD; Sumer Pek, MD; R. Harsha Rao, MD; Philip Raskin, MD; Robert E. Ratner, MD; Victor L. Roberts, MD; Julio Rosenstock, MD; Stephen Schneider, MD; Sherwyn L. Schwartz, MD; Jackie See, MD; John P. Sheehan, MD; William Sivitz, MD; Norman G. Soler, MD, PhD; Bruce Spinowitz, MD; Alain J. Taylon, MD; Timothy O. Wahl, MD; Richard L. Weinstein, MD; S. R. Weiss, MD; and Fred Whitehouse, MD.

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