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Insulin Glargine Compared to NPH Among Insulin-Naïve, U.S. Inner City, Ethnic Minority Type 2 Diabetic Patients

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Abstract

Aims—We compared basal regimens of glargine or NPH among insulin-naïve, U.S. inner city, ethnic minority type 2 diabetic patients who were sub-optimally controlled on maximally tolerated doses of combination oral agents.

Methods—Eighty-five subjects were randomized to 26 weeks of open-label, add-on therapy using single doses of bedtime NPH, bedtime glargine, or morning glargine; initially through an 8-week dose titration phase, followed by a 16-week maintenance phase during which insulin doses were adjusted only to avoid symptomatic hypoglycemia.

Results—All 3 groups were comparable at baseline (mean HbA_{1c} 9.3 ± 1.4%), and improved their HbA_{1c} (to 7.8 ± 1.3%), fasting, and pre-supper glucose readings, with no significant between-group differences. Weight gain was greater with either glargine regimen (+3.1 ± 4.1 kg and +1.7 ± 4.2 kg) compared to NPH (−0.2 ± 3.9 kg), despite comparable total insulin doses. Pre-supper hypoglycemia occurred more frequently with morning glargine, but nocturnal hypoglycemia and improvements in treatment satisfaction did not differ among groups.

Conclusions—Among inner city ethnic minority type 2 diabetic patients in the U.S., we found no differences in basal glycemic control or nocturnal hypoglycemia between glargine and NPH, although glargine precipitated greater weight gain.

Keywords

glargine; ethnicity; low-income

Introduction

Type 2 diabetes mellitus disproportionately affects U.S ethnic minorities [1], such as Hispanics and African-Americans in rapidly growing, inner city communities where low-income and low-educational level ethnic minority individuals are often concentrated. The urban healthcare systems that serve these indigent populations tend to be supported by

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Conflict of Interest

The authors declare that they have no conflict of interest.

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limited resources and restricted drug formularies that are designed principally to contain costs while maximizing treatment efficiency. Achieving optimal use of insulin therapies is particularly challenging for such economically disadvantaged communities where issues such as food insecurity [2,3] and limited or inconsistent access to medication supplies or supportive healthcare services may be obstacles to maintaining optimal control, and yet such patients may stand to benefit a great deal from the powerful benefits of appropriately administered insulin regimens.

The published literature comparing the efficacy of the long-acting insulin analogue glargine against NPH as a basal insulin (without confounding by prandial insulins) in oral agent-treated type 2 diabetic patients has produced inconsistent results in terms of their relative efficacy; the expectation of more effective hemoglobin A_{1c} (HbA_{1c}) control due to the longer action profile of glargine has been demonstrated in a few head-to-head comparison studies [4,5], but not in most others [6–13]. A meta-analysis of published data indicates that there is no overall benefit in terms of improved glucose control [14], while Fritsche *et al.* found that the timing of glargine administration may actually influence its efficacy [5]. We hypothesized that, within the poorly controlled, inner city, low-income ethnic minority community of South Los Angeles, the longer action profile of insulin glargine relative to NPH may result in different efficacy and/or tolerability than what has been reported in other populations, when used as single-dose basal regimens among insulin-naïve subjects inadequately controlled on combination oral agents.

Subjects

We enrolled individuals between the ages of 18 and 75 who had been diagnosed with type 2 diabetes for at least 1 year. Subjects were recruited from the Diabetes Specialty Clinic at the Martin Luther King Jr. Multi-Service Ambulatory Clinic (MLK-MACC) located in South Los Angeles, which serves a large inner city population of low-income and low-educational level ethnic minority (predominantly Hispanic and African-American) patients. To qualify, subjects' baseline HbA_{1c} levels were between 7.5 and 12.0% despite at least 3 months of consistent therapy with maximally tolerated doses of combination oral agents (metformin, sulfonylureas and/or thiazolidinediones; other medication classes are not available through our institution's formulary); subjects' BMIs had to be between 20 and 40 kg/m². Subjects were insulin-naïve other than previous use for gestational diabetes or for less than 1 week during hospitalizations. Subjects were excluded if they had confirmed or suspected type 1 diabetes, advanced proliferative retinopathy, occupations that required night shift work or any diurnal schedules that caused erratic mealtimes, as well as pregnancy, lactation, and any renal, hepatic or other systemic disorders that might complicate glycemic control. The study protocol was reviewed and approved by the Institutional Review Board of Charles R. Drew University of Medicine and Science. This study was investigator-initiated, and its concept, design, conduct, analyses, and manuscript preparation were all under the exclusive control of the author at all times.

Materials and Methods

Study Design and Procedures

Eligible subjects were entered into a 2-week run-in phase of self-glucose monitoring (SMBG) while still taking only their baseline combination oral agents, along with reinforcement of nutritional principles. Daily SMBG was to be performed before each meal, at bedtime, and whenever hypoglycemic symptoms occurred, using the One-Touch Ultra glucose monitor (Lifescan, Milpitas, CA), calibrated as necessary by the research team. Subjects were then randomized to one of three single-dose basal insulin regimens in an open-label fashion: 1) NPH at bedtime, 2) glargine at bedtime, or 3) glargine in the morning;

and taught the techniques of insulin self-administration. All insulin preparations were provided to subjects through the MLK-MACC clinical pharmacy or from a limited supply of glargine provided specifically for this study from the manufacturer (Sanofi-Aventis, Bridgewater, NJ); starting doses were 10 units for non-obese or 16 units for obese subjects. This was followed by an 8-week dose titration phase whereby pre-prandial glucose readings were targeted to achieve at least 50% of readings below 120 mg/dL; NPH and bedtime glargine subjects titrated doses according to fasting readings, while morning glargine subjects titrated doses according to pre-supper readings. All SMBG readings were collected weekly and reviewed by the investigator; insulin doses were titrated at each encounter in increments of 2–4 units for lean subjects or 4–8 units for obese subjects; however, the investigator was permitted to individualize the dosage adjustments at each encounter. Adverse events, including any episodes of symptomatic hypoglycemia were reviewed at each visit, along with subjective recall of the possible contributing factors to all symptomatic hypoglycemic episodes. Hypoglycemia was defined as the occurrence of classic symptoms that were relieved by food intake, with or without a corroborating low glucose reading. Correctable causes of hypoglycemia, such as erratic adherence to diet and lifestyle were identified, and dose adjustments were made in addition to lifestyle counseling, if deemed necessary to avert future occurrences of symptomatic hypoglycemia. A team of study coordinators specific to this study followed all subjects and collected all relevant clinical information at each encounter, including SMBG results, and the investigator then reviewed the data and rendered all clinical decisions.

Following the titration phase, subjects maintained constant insulin doses through a maintenance phase for an additional 16 weeks, with only downward dose adjustments permitted if necessary to avoid repeated episodes of symptomatic hypoglycemia that could not otherwise be prevented through diet and lifestyle counseling; SMBG results were reviewed bi-weekly through the maintenance phase. All oral agents were maintained at constant dosages throughout the entire 26-week trial, and standardized nutritional counseling was reviewed and reinforced with all subjects at each encounter. Key outcomes were assessed at baseline, at the end of the titration phase (week 10), and the end of the maintenance phase (week 26); HbA_{1c} was additionally assessed at the midpoint of the maintenance phase (week 18).

Outcomes

The primary outcome was the between-group difference in the change of HbA_{1c} from baseline. Secondary outcomes included the between-group differences in the proportion of subjects achieving HbA_{1c} ≤ 7.0% by week 26; the change in fasting SMBG readings and the percentage of readings that achieved the ADA-recommended target of <130 mg/dL between the run-in phase and the study's end; the change in pre-supper SMBG readings and the percentage of readings that achieved <130 mg/dL between the run-in phase and the study end; incidence of hypoglycemic events at each diurnal monitoring time point (pre-meal, bedtime, or overnight) and total events pooled across all diurnal time points; the proportion of subjects reporting any hypoglycemia; changes in weight and BMI; insulin dose expressed as absolute units as well as relative to body weight; and perceptions of treatment satisfaction using the validated Diabetes Treatment Satisfaction Questionnaire (DTSQ) Status and Change forms [15], administered at baseline and the study's end, respectively. All counseling and follow-up, as well as DTSQ questionnaires, were provided in Spanish for those Hispanic subjects not sufficiently fluent in English. All HbA_{1c} measurements were performed by the MLK-MACC clinical chemistry laboratory, utilizing an HPLC method that conforms to the DCCT standard.

Data Analyses and Statistics

All data were analyzed by an intent-to-treat paradigm as a primary analysis using last-value-carried-forward imputation of incomplete data, along with a secondary per-protocol analysis that examined only subjects who completed the full duration of the study. Baseline comparisons were made using the Kruskal-Wallis test for continuous variables and the χ^2 test for categorical variables. All continuous outcome variables were analyzed by repeated measures ANOVA for the group $\times$ time interaction, with the Greenhouse-Geisser correction if necessary. Hypoglycemic event rates were analyzed across groups using the Kruskal-Wallis test, proportions of subjects were analyzed using the χ^2 test, and DTSQ scores using ANCOVA. Based on our previously published HbA_{1c} levels in oral agent-treated patients from our clinic [16], enrollment of 24 subjects in each of the 3 treatment arms (72 subjects total) would provide 95% power to detect an HbA_{1c} difference of 0.8%, at a 5% significance level.

Results

Subjects

Enrollment began in September 2002 but was terminated in February 2009 due to funding limits. Out of all patients referred to the study, 108 subjects qualified and agreed to participate, of whom 85 were randomized (Figure 1). Of the 23 qualifying subjects who failed to reach randomization, 9 were withdrawn due to protocol violations prior to randomization (medication or SMBG noncompliance despite extensive counseling), 8 were dropped because of substantial improvements in dietary compliance that precipitated hypoglycemia and obviated the need for insulin, 5 were lost to follow-up for unknown reasons, and 1 subject withdrew voluntarily. Baseline characteristics of all qualifying subjects are shown in Table 1. Among the randomized subjects, there were no statistically significant differences across the 3 treated groups; mean diabetes duration was 8.7 years, and mean HbA_{1c} was 9.3%. Subjects who were withdrawn before reaching randomization did not differ from the randomized subjects except that their baseline HbA_{1c} level was modestly lower than the 3 treated groups.

Glycemic Control

The primary outcome of HbA_{1c} improved in all treatment groups, to an overall mean of 7.8 ± 1.3 %, with no significant difference among groups when assessed by repeated measures ANOVA for the group $\times$ time interaction (Table 2). There were also no differences in the proportions of subjects achieving HbA_{1c} ≤ 7.0 % by study end (23%, 23% and 28% for NPH, bedtime glargine, and morning glargine, respectively). Secondary outcomes of fasting and pre-supper SMBG readings, as well as the percentages of those readings <130 mg/dL also improved, with no significant between-group differences in the overall group $\times$ time interaction. For these glycemic outcomes, the greatest improvement occurred between baseline and the end of the titration phase (week 10), with substantially less additional improvement occurring through the maintenance phase.

Weight Gain and Insulin Dose

Weight gain was modestly but significantly greater for both of the glargine groups (averaging 1.7 kg for the bedtime glargine group and 3.1 kg for the morning glargine group), as compared to the NPH group (averaging a loss of 0.2 kg; Table 2); the weight gain difference between the two glargine groups was not significant. Because insulin-associated weight gain can be exacerbated by thiazolidinediones, and because there were non-significant differences in thiazolidinedione use among the groups at baseline, we also applied a linear regression model to adjust the weight and BMI differences for

thiazolidinedione use, and found that the significance levels changed only minimally, indicating that thiazolidinedione use did not explain the significant differences in weight gain. These weight gain differences were also not associated with a higher overall dose of insulin, either in terms of total units of insulin or units per kg body weight required by the end of the study.

Hypoglycemia

Symptomatic hypoglycemia rates varied between 6.7 to 9.6 events per patient through the 6-month study, or 13.4 to 19.2 events per patient-year, which did not differ significantly across groups (Table 3). Between 77% and 96% of subjects reported at least one hypoglycemic episode, also a non-significant difference across groups. When separated by time of day, however, hypoglycemia was more frequent and affected more subjects using morning glargine at the pre-supper hours, and affected more subjects at the bedtime hours, but there were no differences in nocturnal or fasting hypoglycemia between glargine and NPH, even when overnight and fasting events were combined. No severe hypoglycemic events were reported.

Treatment Satisfaction

Treatment satisfaction scores on the DTSQ improved significantly across all groups, with no between-group differences with respect to any of the eight items on the DTSQ, or on a combined score (data not shown).

Secondary Analyses

Despite extensive efforts by the study coordinators to maintain strict compliance with insulin, concurrent oral agents, SMBG, and scheduled follow-up throughout the study, 34 of the randomized subjects failed to complete the study in its entirety, including 26 who were withdrawn due to protocol violations (Figure 1). However, secondary per-protocol analyses based only on the completed subjects did not substantially change the statistical significance of the HbA_{1c}, fasting and pre-supper SMBG, weight gain, insulin dose, nocturnal hypoglycemia and treatment satisfaction findings presented above. The difference in pre-supper hypoglycemia became non-significant in the secondary analysis, but the difference in bedtime hypoglycemia remained significant (data not shown).

Discussion

The low-income, ethnic minority diabetic population of U.S. inner cities is affected by unique socioeconomic and cultural factors that can adversely impact good glycemic control. Food insufficiency is known to be most prevalent in economically disadvantaged communities [2], particularly Mexican-American households without health insurance [3]. Such circumstances are associated with lower nutrient intake [17], compensatory feeding practices to increase energy intake [18], and among insulin-requiring diabetic individuals, frequent hypoglycemia attributed to the inability to afford food [19]. In addition, these communities are often served by resource-limited healthcare systems that emphasize the differential costs between insulin analogues like glargine and NPH. Previous comparisons of the cost-effectiveness of these two insulins have yielded conflicting conclusions [20–23], and no studies have focused on their effectiveness within resource-limited, inner city healthcare systems. We hypothesized that given the uniqueness of inner city populations, glargine might have a different efficacy and/or tolerability than NPH. However, consistent with the observations of others [6–14], we also found no significant differences in overall glycemic control between the two preparations.

Weight Changes

We did find that glargine conferred a modest but significantly greater weight gain than NPH, independent of overall dose requirements. This is contrary to the findings from other studies of similar design [5,6,8–13] that found either the opposite to be true, or no difference in weight gain. However, our findings do agree with those of the comprehensive meta-analysis of Bazzano *et al.* [14]. It is possible that, with the higher-energy foods and erratic dietary patterns typical of low-income, food-insecure populations, an insulin formulation that acts through the daytime hours may precipitate more weight gain than bedtime NPH whose effect wanes through the daytime hours.

Hypoglycemia

Overall, our rates of hypoglycemia were actually higher than other similar trials, measured either as events per patient-year (13.4 to 19.2 compared to <10 in other reports [4, 6, 7]) or as the percentage of subjects reporting any hypoglycemia (77 to 96% compared to ≤75% in other reports [5–7, 9–12, 14]). This occurred in spite of our titration target being less aggressive than that of some other trials [5–8], and in spite of our relatively modest insulin doses (averaging 0.2 units/kg). This may also be a reflection of our subjects' erratic daytime dietary patterns. And in spite of this higher overall propensity for hypoglycemia, we did not find a significant difference in nocturnal hypoglycemia (including overnight and fasting events combined) between glargine and NPH, in contrast to all other reports [4–14], even though fasting event rates appeared to be non-significantly higher with NPH compared to bedtime glargine. While the study may have been under-powered to detect smaller differences in the incidence of nocturnal hypoglycemia, our observations may also reflect greater daytime carbohydrate intake in response to daytime hypoglycemia (particularly with morning glargine) that then mitigates any nocturnal hypoglycemia, or alternatively, fear of nocturnal hypoglycemia that leads to larger, carbohydrate-rich bedtime snacks. Anecdotally, fear of nocturnal hypoglycemia was expressed during counseling by some of our patients taking bedtime insulin.

Timing of Glargine

We did not find a significant difference in glycemic control between morning and bedtime use of glargine, contrary to the observations of Fritsche *et al.* [5], who had suggested that less aggressive titration of bedtime glargine out of fear of nocturnal hypoglycemia might have biased their findings in favor of daytime glargine (even though their insulin doses were not different, as in our study). We did observe a non-significantly greater decrement in HbA_{1c} with morning glargine than bedtime glargine (−1.9% vs. −1.3%), so perhaps with greater statistical power, we might have replicated their findings. In addition, we targeted morning glargine doses to pre-supper instead of fasting readings, and since pre-supper readings are often higher, this might have also biased our findings in favor of morning glargine; the lack of a difference in insulin dosage still argues against this explanation, although it is consistent with our slightly higher pre-supper and bedtime hypoglycemia rate with morning glargine.

Study Limitations

Our study was limited to a single center, focusing on a unique population, and thus enrolled fewer subjects as compared to other trials [4,5,7–12]. As a result, we cannot rule out the possibility of a more subtle difference between these insulin regimens that we were unable to detect. The highly prevalent cultural myths in this population that surround insulin use and our patients' reluctance to accept insulin based on those myths also severely curtailed our enrollment and contributed to our relatively high non-completion rate, which we had underestimated. There were substantial challenges in maintaining strict compliance with all

study requirements throughout the trial, despite extensive efforts by study coordinators to educate and keep close contact with all subjects. Despite these challenges, our principal findings did not substantially change when we analyzed only the completed subjects in the secondary analyses, suggesting that our negative findings were not due to bias from poor subject compliance or high dropouts, but that they do indeed reflect the relative utility of these basal insulins for this unique demographic group. Ideally, however, our findings should be verified by a larger, follow-up trial in populations with similar demographic characteristics. We also acknowledge that by prohibiting upward dose titration during the maintenance phase, which was necessary to detect any HbA_{1c} differences among the insulin regimens once SMBG targets were reached, our conclusions may not necessarily apply to clinical practices that emphasize intensification of insulin over intensification of dietary and lifestyle skills.

Summary

We found that among the inner city, ethnic minority type 2 diabetic patients of South Los Angeles who are starting insulin, there were no differences in basal glycemic control between insulin glargine and traditional NPH. In fact, glargine may be detrimental by precipitating greater weight gain, and the specific advantage of less nocturnal hypoglycemia seen in other studies may not hold true for this population. These findings may be useful for similar healthcare systems that serve low-income, indigent, minority populations for establishing evidence-based policies regarding cost-effective medication supply and coverage.

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Figure 1.

Flowchart of Enrolled Subjects. * Protocol violations included confirmed noncompliance with insulin or concurrent oral agents for ≥ 2 weeks; SMBG occurring less than once daily for 4 or more days per week over 2 consecutive scheduled visits; or any verified falsification of SMBG readings.

Table 1

Baseline Characteristics of All Qualifying Subjects

	NPH hs	Glargine hs	Glargine AM	p *	Pooled	Not Randomized
n	30	30	25		85	23
Age (Years)	53.2 ± 7.7	50.3 ± 11.2	53.0 ± 8.6	NS	52.1 ± 9.3	56.8 ± 10.1
Gender (Female/Male)	21/9	15/15	13/12	NS	49/36	15/8
Ethnicity: n (%)						
Hispanic	25 (83)	24 (80)	21 (84)	NS	70 (82)	20 (87)
African-American	4 (13)	5 (17)	3 (12)	NS	12 (14)	3 (13)
Other	1 (3)	1 (3)	1 (4)	NS	3 (4)	0 (0)
Diabetes Duration (Years)	7.8 ± 4.2	9.0 ± 5.9	9.5 ± 5.2	NS	8.7 ± 5.1	8.0 ± 5.8
Oral Agents: n (%)						
Metformin	30 (100)	29 (97)	24 (96)	NS	83 (98)	20 (87)
Sulfonylureas	29 (97)	30 (100)	25 (100)	NS	84 (99)	21 (91)
Thiazolidinediones	18 (60)	27 (90)	20 (80)	NS	65 (76)	12 (52)
Weight (kg)	82.6 ± 18.1	85.0 ± 15.0	82.7 ± 14.3	NS	83.5 ± 15.9	82.4 ± 14.4
BMI (kg/m ²)	32.1 ± 6.0	31.6 ± 5.0	31.1 ± 5.2	NS	31.6 ± 5.4	31.8 ± 5.7
HbA _{1c} (%)	9.3 ± 1.6	9.2 ± 1.3	9.6 ± 1.2	NS	9.3 ± 1.4	8.8 ± 1.9
FPG (mg/dL)	175 ± 48	189 ± 60	174 ± 59	NS	179 ± 56	170 ± 66

* p value across treatment groups by Kruskal-Wallis test (for continuous variables) or χ^2 test (for categorical variables). AM, morning; FPG, fasting plasma glucose; hs, bedtime, NS, not significant.

Table 2

Results for Glycemia, Weight and Insulin Doses by Study End

	NPH hs	Glargine hs	Glargine AM	p
HbA _{1c} at Baseline (%):	9.3 ± 1.6	9.2 ± 1.3	9.6 ± 1.2	
Week 10	7.7 ± 1.0	8.0 ± 1.4	7.8 ± 1.1	
Week 18	7.9 ± 1.5	7.9 ± 1.4	7.7 ± 1.1	
Week 26	7.9 ± 1.5	7.9 ± 1.4	7.6 ± 1.1	
Δ From Baseline:	-1.4 ± 1.7 [*]	-1.3 ± 1.2 [*]	-1.9 ± 1.4 [*]	NS [†]
HbA _{1c} ≤7.0% (% of Subjects):	23.3	23.3	28.0	NS [‡]
FPG by SMBG at Run-In Phase (mg/dL):	147 ± 40	171 ± 48	149 ± 40	
Week 10	114 ± 21	128 ± 33	116 ± 30	
Week 26	113 ± 19	125 ± 27	115 ± 24	
Δ From Run-In Phase:	-33 ± 39 [*]	-46 ± 45 [*]	-34 ± 33 [*]	NS [†]
FPG <130 mg/dL by Week 26 (% of Readings):	72.6 ± 22.7	61.7 ± 22.8	73.0 ± 25.1	
Δ From Run-In Phase:	+33.4 ± 31.8 [*]	+34.2 ± 32.0 [*]	+37.0 ± 29.5 [*]	NS [†]
Pre-Supper SMBG at Run-In Phase (mg/dL):	165 ± 61	192 ± 65	154 ± 63	
Week 10	152 ± 30	162 ± 44	140 ± 40	
Week 26	143 ± 25	150 ± 41	127 ± 29	
Δ From Run-In Phase:	-23 ± 61	-43 ± 60 [*]	-26 ± 58	NS [†]
Pre-Supper SMBG <130 mg/dL by Week 26 (% of Readings):	45.5 ± 24.8	45.1 ± 25.3	62.5 ± 22.3	
Δ From Run-In Phase:	+22.1 ± 29.8 [*]	+26.2 ± 31.7 [*]	+21.4 ± 28.6	NS [†]
Weight at Week 26 (kg):	82.4 ± 17.4	86.7 ± 15.0	85.8 ± 16.0	
Δ From Baseline:	-0.2 ± 3.9	+1.7 ± 4.2	+3.1 ± 4.1	0.01 [†]
BMI at Week 26 (kg/m ²):	32.0 ± 5.8	32.3 ± 5.2	32.2 ± 5.7	
Δ From Baseline:	-0.0 ± 1.5	+0.7 ± 1.6	+1.1 ± 1.4	0.02 [†]
Absolute Insulin Dose by Week 26 (Units):	14.6 ± 13.4	17.7 ± 10.1	17.9 ± 14.4	NS [†]
Relative Insulin Dose by Week 26 (Units/kg):	0.19 ± 0.20	0.20 ± 0.11	0.21 ± 0.16	NS [†]

* p <0.01 for linear trend from baseline or run-in phase to Week 26;

[†] p value by repeated measures ANOVA for the group × time interaction;

[‡] p value by χ^2 test. AM, morning; FPG, fasting plasma glucose; hs, bedtime, NS, not significant; SMBG, self-monitored blood glucose.

Table 3**Hypoglycemic Event Rates and Percent of Subjects Reporting Hypoglycemia**

	NPH hs	Glargine hs	Glargine AM	p[*]
Fasting	4.2 (60)	1.8 (60)	3.2 (80)	NS (NS)
Pre-Lunch	1.4 (43)	2.7 (53)	2.5 (72)	NS (NS)
Pre-Supper	1.6 (40)	1.6 (47)	2.7 (80)	0.02 (0.007)
Bedtime	0.8 (27)	0.4 (10)	0.8 (40)	NS (0.04)
Overnight	0.3 (10)	0.2 (13)	0.3 (20)	NS (NS)
Fasting + Overnight	4.5 (63)	2.0 (60)	3.5 (80)	NS (NS)
All Events	8.2 (77)	6.7 (77)	9.6 (96)	NS (NS)

Results expressed as mean number of events per patient over the entire study duration (percent of subjects reporting any symptomatic hypoglycemic event);

* p for event rate by Kruskal-Wallis test (p for percent of subjects by χ^2 test). AM, morning; hs, bedtime; NS, not significant.