Comparison of Glycemic Variability Associated With Insulin Glargine and Intermediate-Acting Insulin When Used as the Basal Component of Multiple Daily Injections for Adolescents With Type 1 Diabetes

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OBJECTIVE — To compare the glucose variability associated with insulin glargine and NPH/Lente insulin used as the basal insulin component of a multiple daily injection (MDI) regimen in pediatric patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Continuous glucose monitoring data were collected from a subset of patients ($n = 90$) who agreed to use a continuous glucose monitoring system during an active-controlled, randomized, open-label study evaluating the safety and efficacy of insulin glargine and NPH/Lente insulin used with insulin lispro as part of an MDI regimen.

RESULTS — Treatment with insulin glargine resulted in significant reductions in glucose variability as measured by the SD of glucose values (adjusted mean change from baseline to week 24: −13.4 mg/dl [−0.74 mmol/l]; $P \leq 0.05$), mean amplitude of glycemic excursion (−34.4 mg/dl [−1.91 mmol/l]; $P \leq 0.0001$), and *M* value (−9.6 mg/dl [−0.53 mmol/l]; $P \leq 0.03$). The corresponding reductions in glucose variability for NPH/Lente were not significant.

CONCLUSIONS — Insulin glargine is associated with greater reductions in glucose variability than NPH/Lente insulin in pediatric patients with type 1 diabetes.

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Improved glycemic control to prevent or delay microvascular complications is of paramount importance in children and adolescents with type 1 diabetes but is often achieved at the price of increased hypoglycemia (1,2). Persistent wide fluctuations in plasma glucose in the presence of lower mean glucose and A1C values may be an important reason why intensive therapy, as practiced in the Diabetes Control and Complications Trial, increases the risk of severe hypoglycemia (2,3). Several studies have suggested that glycemic variability may also play an independent role in the development of diabetes complications (4–8). Therefore, some investigators suggest that blood glucose variability, when combined with A1C levels, is an important indicator of glycemic control and the risk for long-term complications (9,10).

Insulin glargine (Lantus; sanofi-aventis U.S., Bridgewater, NJ) is a basal insulin with little or no pronounced action peak and limited site absorption variation (11). Its use as part of a multiple daily injection (MDI) regimen demonstrated good glucose control with less hypoglycemia than NPH insulin in adults with type 1 or type 2 diabetes (12,13). However, only one major randomized clinical trial in pediatric patients has examined the relative efficacy of insulin glargine–based MDI versus MDI regimens utilizing intermediate-acting insulins, and this study did not examine glucose variability (14).

Consequently, we performed a large randomized clinical trial in adolescents with type 1 diabetes to compare these two approaches to intensive insulin therapy. A secondary aim of this trial was to compare the glucose variability using insulin glargine with that using intermediate-acting insulin (NPH or Lente) as the basal insulin component of an MDI regimen. Both patient groups received premeal insulin lispro (Humalog; Eli Lilly and Co., Indianapolis, IN). This study reports the results of data analysis from a subset of patients who volunteered to use a continuous glucose monitoring system (CGMS) to assess glucose variability. Results from the entire randomized controlled trial are reported elsewhere (15).

RESEARCH DESIGN AND METHODS

— The study design and methods have been described previously (15). Patients with type 1 diabetes ($n = 175$) participated in this randomized study comparing insulin glargine and NPH/Lente insulin, each used with premeal insulin lispro in an MDI regimen. A subset of patients (glargine, $n = 74$; NPH/

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Table 1—*Adjusted mean change from baseline in time spent above or below specified sensor glucose levels in CGMS subset*

	Insulin glargine			NPH/Lente			Difference	
	n	Sample mean (min/day)	*P* vs. baseline	*n*	Sample mean (min/day)	*P* vs. baseline	Adjusted mean	*P*
<70 mg/dl (<3.89 mmol/l)								
Baseline	45	119.0		45	75.5			
Week 12	39	141.0	0.1067	35	94.8	0.7013	30.4	0.4040
Week 24	33	64.2	0.0983	36	85.3	0.5931	−46.6	0.1163
<50 mg/dl (<2.78 mmol/l)								
Baseline	45	25.1		45	18.2			
Week 12	39	54.0	0.0288	35	38.6	0.1508	10.9	0.6315
Week 24	33	13.4	0.5246	36	39.8	0.0083	−38.2	0.0198
≤40 mg/dl (≤2.22 mmol/l)								
Baseline	45	12.7		45	6.9			
Week 12	39	27.4	0.0832	35	21.6	0.2550	5.9	0.7089
Week 24	33	3.0	0.3597	36	23.8	0.0092	−26.9	0.0130
≥250 mg/dl (≥13.88 mmol/l)								
Baseline	45	397.3		45	415.4			
Week 12	39	289.9	0.0220	35	408.3	0.7453	−93.8	0.1756
Week 24	33	302.1	0.0347	36	390.9	0.4545	−69.2	0.3013
≥350 mg/dl (≥19.43 mmol/l)								
Baseline	45	107.0		45	106.9			
Week 12	39	54.4	0.0126	35	109.2	0.7910	−56.7	0.1214
Week 24	33	66.6	0.0709	36	87.9	0.2916	−18.1	0.5523

Lente, $n = 75$) volunteered to use the CGMS (Medtronic/MiniMed, Northridge, CA), which measures interstitial glucose concentrations every 5 min for 3 days via a glucose oxidase–based method, to compare variability in interstitial glucose levels across the two regimens. CGMS accuracy has been demonstrated to be similar from day to day (16). The median relative absolute difference between sensor and reference plasma glucose values in children with type 1 diabetes has been 11% during outpatient use (17). In this study, patients and the health care team were blinded to CGMS results, which were not used for diabetes management but only for the assessment of glycemic variability.

Eligibility criteria and baseline characteristics

Patients aged 9–17 years with type 1 diabetes (for ≥1 year), at Tanner stage ≥2 puberty, with A1C level 7.0–9.5%, and at least two insulin injections per day or continuous subcutaneous insulin infusion were enrolled. Excluded were patients with diabetic ketoacidosis in the past 3 months or two or more episodes of severe hypoglycemia (i.e., an event requiring the assistance of another person and accompanied by either a blood glucose level of <36 mg/dl [<2.0 mmol/l] or prompt recovery after oral carbohydrate intake, intravenous glucose, or glucagon administration) in the past 12 months. Patients had to be willing to perform self-monitoring of blood glucose (SMBG) at least four times daily. The CGMS subgroup had to be willing to use the MiniMed CGMS for up to 3 consecutive days on three occasions.

Study medication

Patients were randomized to receive either basal insulin glargine once daily before breakfast or intermediate-acting insulin (NPH or Lente) twice daily; starting doses were 40–50% of the total daily insulin dose. Both groups received insulin lispro before each meal based on carbohydrate intake, with individualized correction doses based on the degree to which blood glucose levels deviated from the target glucose values.

Continuous glucose monitoring

Interstitial glucose was measured during three periods (week 0, week 12, and week 24) for 3 consecutive days each. Patients were to enter at least four SMBG values daily to calibrate the CGMS and to record important events (e.g., insulin boluses, snacks, and exercise).

Measures of glycemic control and glycemic variability

Glycemic control was assessed by A1C at baseline, 12 weeks, and 24 weeks and by the time CGMS glucose values were <70, <50, ≤40, ≥250, and ≥350 mg/dl (<3.89, <2.78, ≤2.22, ≥13.88, and ≥19.45 mmol/l) (refer to Table 1). A1C was measured using ion-exchange high-performance liquid chromatography with the Bio-Rad Variant II Turbo analyzer (Bio-Rad, Hercules, CA). The system was certified by the National Glycohemoglobin Standardization Program with values traceable to the Diabetes Control and Complications Trial reference method; the reported normal range is 4.27–6.07%, with coefficients of variation of 1.94 and 2.58% at A1C values of 6.25 and 12.5%, respectively.

Measures of glucose variability from the CGMS were *1*) SD of the mean of the sensor values, *2*) mean amplitude of glycemic excursion (MAGE) (18,19), and *3*) *M* value, which is expressed by the formula below (19).

$$\left(\frac{\sum}{N} \left| 10 \log \frac{Sensor\ glucose}{120} \right|^3 + \frac{(Max - Min\ Sensor\ glucose)}{20} \right)$$

Table 2—*Demographics, baseline characteristics of randomized patients, and CGMS subpopulation (ref. 24)

	Study population		CGMS subpopulation	
	Insulin glargine	NPH/Lente	Insulin glargine	NPH/Lente
n	85	90	45	45
Age (years)	13.1 ± 2.4	13.4 ± 2.4	13.2 ± 2.3	13.4 ± 2.5
Sex (female)	45 (53.6)	44 (52.4)	23 (51.1)	19 (42.2)
Race/ethnicity				
Caucasian	71 (84.5)	68 (81.0)	41 (91.1)	40 (88.9)
African American	0 (0.0)	7 (8.3)	0 (0.0)	0 (0.0)
Asian	2 (2.4)	2 (2.4)	0 (0.0)	2 (4.4)
Hispanic	7 (8.3)	2 (4.8)	3 (6.7)	2 (4.4)
Multiracial/multiethnic	2 (2.4)	1 (1.2)	1 (2.2)	0 (0.0)
Other	2 (2.4)	2 (2.4)	0 (0.0)	1 (2.2)
Weight (kg)	57.2 ± 14.8	59.1 ± 18.1	57.9 ± 15.1	57.8 ± 19.4
BMI (kg/m^2)	22.6 ± 3.8	22.9 ± 5.0	22.6 ± 0.8	22.6 ± 0.9
Age at onset (years)	8.5 ± 3.5	8.5 ± 3.7	8.3 ± 3.7	9.0 ± 3.5
Duration of diabetes (years)	5.1 ± 3.4	5.4 ± 3.7	5.4 ± 3.7	4.9 ± 3.6
A1C (%)				
Baseline	7.8 ± 0.8	8.0 ± 0.8	7.9 ± 0.9	8.0 ± 0.8
Adjusted baseline				
A1C 10th percentile	7.28	7.12	7.28	6.95
A1C median percentile	7.74	7.86	7.82	7.84
A1C 90th percentile	8.32	8.79	8.51	8.97
Baseline fasting SMBG (mg/dl)	188.5 ± 54.4	203.0 ± 52.1	187.4 ± 62.5	203.4 ± 42.3

Data are means, means ± SD, or *n* (%). Adjusted mean values of A1C are at study end in relation to baseline values. *No significant differences between groups who did or did not participate in CGMS.

Minutes spent at glucose levels <70, <50, ≤40, ≥250, and ≥350 mg/dl (<3.89, <2.78, ≤2.22, ≥13.88, and ≥19.45 mmol/l) were calculated.

For CGMS data to be analyzable, each patient had to have a sufficient duration (i.e., 24 h of sensor data for each day) of CGMS data and a date for CGMS data collection at the appropriate time in the study. Some patients in the insulin glargine ($n = 29$) and the NPH/Lente ($n = 30$) groups were excluded from the analysis because of discrepancies between CGMS and SMBG values recorded by the same patient, unfamiliarity with the mechanics of the CGMS, or technical problems during CGMS measurement. Forty-five patients in each group had analyzable data at baseline and at any end point, and 33 patients in the glargine group and 36 in the NPH/Lente group had data at baseline and week 24.

RESULTS — Study results from the overall trial are reported elsewhere (15). In summary, change in A1C level from baseline to 24 weeks was −0.25 ± 0.14% for the glargine group ($n = 76$) and −0.05 ± 0.13% for the NPH/Lente group ($n = 81$); these changes were not significant ($P = 0.1725$). However, repeated-measures analysis showed a greater reduction in A1C level associated with the use of insulin glargine in patients who had higher baseline A1C values (for median and 90th percentile values; $P < 0.05$ between groups). Rates of glucose readings <70 mg/dl (3.88 mmol/l) (per patient-year) were 116.1 and 93.8 in the glargine and the NPH/Lente group, respectively ($P = 0.030$), whereas rates of glucose <50 mg/dl (2.78 mmol/l) (21 in glargine group vs. 20 in NPH/Lente group; $P = 0.81$) and <36 mg/dl (2.0 mmol/l) (1.2 vs. 1.7; $P = 0.32$), severe hypoglycemia (0.20 vs. 0.09; $P = 0.18$), and treatment-emergent adverse events (17.6 vs. 8.9%; $P = 0.12$) did not differ significantly between groups.

Patient characteristics at baseline

There were no significant differences in baseline characteristics between patients who used the CGMS and the entire study population (Table 2). There also was no significant difference between the main study group and CGMS subgroup with respect to changes in A1C level during the trial (Table 1).

Glycemic outcomes

In the CGMS subgroup, the adjusted mean change in A1C level from baseline to end point was −0.12% and −0.10% for glargine versus NPH/Lente, respectively ($P = 0.9250$). A1C outcomes and hypoglycemia rates (events per patient-year, determined by glucose meter measurements) in the CGMS subgroup paralleled those in the overall study (15).

Continuous glucose monitoring values and variability

Mean glucose value. There were no between-group differences in mean 24-h glucose concentrations (Table 3; Fig. 1) or the glucose concentrations analyzed in 6-h intervals throughout the day (data not shown).

SD of glucose. Subjects using insulin glargine showed a significant reduction in glucose variability (as measured by SD) from baseline ($P < 0.0001$ for each time point) and a significantly greater reduction at week 24 than those using NPH/Lente ($P = 0.0147$) (Table 3; Fig. 2*A*). Those using NPH/Lente had a trend for reduction in SD from baseline at week 12 ($P = 0.0503$) but not at week 24 ($P = 0.4286$) (Table 2; Fig. 2*A*).

Table 3—*Mean CGMS sensor values and variability measures at baseline and weeks 12 and 24*

	Insulin glargine			NPH/Lente			
	n	Sample mean (mg/dl)	*P* vs. baseline	*n*	Sample mean (mg/dl)	*P* vs. baseline	*P* for difference*
Mean CGMS sensor values							
Baseline	45	190.6		45	197.1		
Week 12	39	177.3	0.0728	35	195.4	0.6759	0.3516
Week 24	33	181.8	0.2228	36	195.3	0.6371	0.5745
SD							
Baseline	45	77.4		45	73.9		
Week 12	39	63.8	<0.0001	35	71.2	0.0503	<0.0509
Week 24	33	64.2	<0.0001	36	74.3	0.4286	0.0147
MAGE							
Baseline	45	188.5		45	177.7		
Week 12	39	154.7	0.0001	35	173.6	0.1139	0.1051
Week 24	33	152.0	<0.0001	36	182.0	0.7459	0.0055
M value							
Baseline	45	43.5		45	43.2		
Week 12	39	36.8	0.0309	35	43.7	0.8440	0.1768
Week 24	33	34.2	0.0048	36	42.3	0.7360	0.0631

*Difference in adjusted mean change between groups.

MAGE. MAGE was significantly reduced in the insulin glargine group at weeks 12 ($P = 0.0001$) and 24 ($P < 0.0001$) compared with baseline (Table 2). The adjusted mean change from baseline in MAGE for NPH/Lente-treated patients was not significant at week 12 ($P = 0.1139$) or 24 ($P = 0.7459$). The between-group difference in adjusted mean change in MAGE from baseline favored glargine at week 12 and was significant at week 24 ($P = 0.0055$) (Fig. 2*B*).

***M* value.** Although between-group differences in the adjusted mean reduction in *M* value were not statistically significant (Fig. 2*C*), insulin glargine–treated patients experienced significant reductions from baseline at weeks 12 ($P = 0.0309$) and 24 ($P = 0.0048$) (Table 3). The adjusted mean change from baseline in the NPH/Lente group was not significant ($P = 0.8440$ and $P = 0.7360$ at 12 and 24 weeks, respectively).

Hypoglycemia and hyperglycemia as determined by CGMS

Compared with NPH/Lente, insulin glargine therapy reduced the time spent at glucose levels <70, <50, and ≤40 mg/dl (<3.89, <2.78, and ≤2.22 mmol/l) between baseline and week 24 (Table 1). Differences in adjusted mean change from baseline were statistically significant for insulin glargine for glucose levels <50 mg/dl (<2.78 mmol/l; $P = 0.0198$) and ≤40 mg/dl (≤2.22 mmol/l; $P = 0.0130$). Insulin glargine also significantly reduced the time spent at glucose levels ≥250 and ≥350 mg/dl (≥13.88 and ≥19.43 mmol/l) between baseline and week 12 ($P = 0.0220$ and $P = 0.0126$, respectively); at week 24, time spent ≥250 mg/dl (≥13.88 mmol/l) was also significantly reduced ($P = 0.0347$), but the time spent ≥350 mg/dl (≥19.43 mmol/l; $P = 0.0709$) was not. For NPH/Lente, time spent ≥350 mg/dl (≥19.43 mmol/l) or ≥250 mg/dl (≥13.88 mmol/l) was not reduced at 12 or 24 weeks, and there were no between-group differences ($P = 0.1214$–0.5523 for all).

CONCLUSIONS

The most important finding of this substudy was that pediatric patients receiving insulin glargine appeared to experience less variability in glucose levels, as assessed by SD and MAGE, than patients receiving NPH/Lente insulin. Reductions in glycemic variability may have important clinical implications, including tighter glycemic control with less risk of hypoglycemia and a reduction in vascular complications (3,19). Cox et al. (20) found that high glucose variability precedes severe hypoglycemia, suggesting that reducing glucose fluctuations may reduce the risk for severe hypoglycemia. Hypoglycemia limits the ability to control blood glucose and A1C levels in insulin-treated diabetes (21). Increased glycemic variability, independently of average blood glucose and A1C levels, is believed by some to contribute to vascular complications (22,23). Thus, information on variability of blood glucose may become increasingly important to clinicians and patients in the future; CGMS may serve as a valuable tool for assessing the overall level of glycemic control beyond what can be determined by measuring A1C levels alone. The CGMS with masked 5-min sampling used in this study provides a better estimate of the magnitude of glucose excursions than the fixed-point-in-time 8-point testing procedures used in other studies (3).

In the CGMS subpopulation in this study, despite similar reductions in A1C (−0.12 vs. −0.10%), the adjusted mean difference from baseline at 24 weeks in time spent at glucose levels of ≤40 and <50 mg/dl (≤2.22 and <2.78 mmol/l) by patients using insulin glargine was significantly less than time spent by those using NPH/Lente (13.4 vs. 39.8 min/day, $P = 0.0198$ for glucose <50 mg/dl [<2.78 mmol/l]; and 3.0 vs. 23.8 min/day, $P = 0.013$ for glucose ≤40 mg/dl [≤2.22 mmol/l]). The time spent <70 mg/dl was similar between groups (64.2 vs. 85.3 min/day; $P = 0.1163$) (Table 1). In both groups there was an initial trend for an increase in time at each hypoglycemia threshold at week 12, followed by a reduction by week 24, as noted above. This increase may reflect the initial uptitration of insulin doses at the start of the study, followed by stabilization of doses. There were too few severe hypoglycemic events to allow identification of differ-

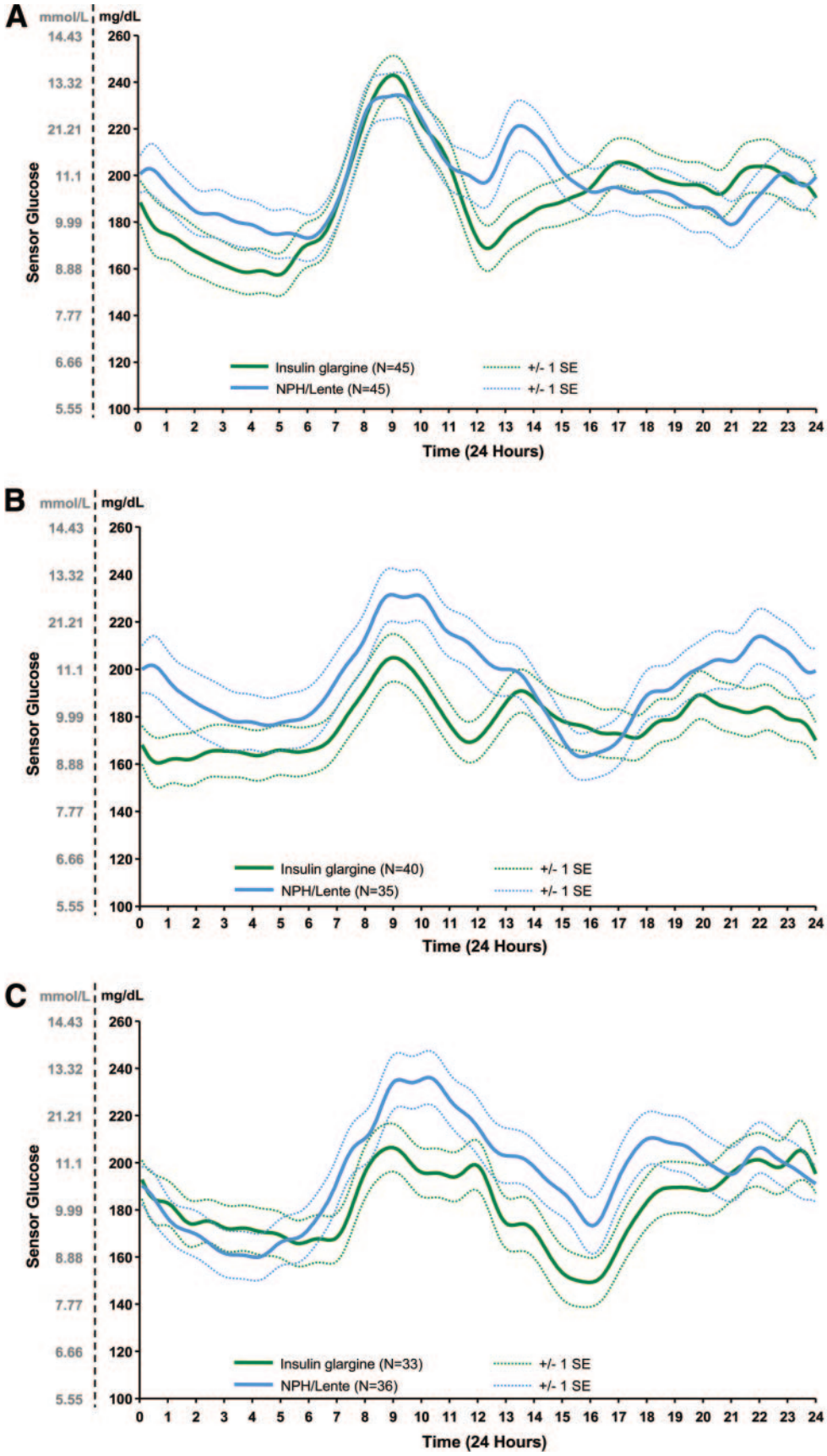

Figure 1—*Mean (±1 SE) CGMS curves in patients with at least one 24-h CGMS recording at the following time points: baseline* (A)*, week 12* (B)*, and week 24* (C) *for those in the glargine group (green) and the NPH/Lente group (blue).*

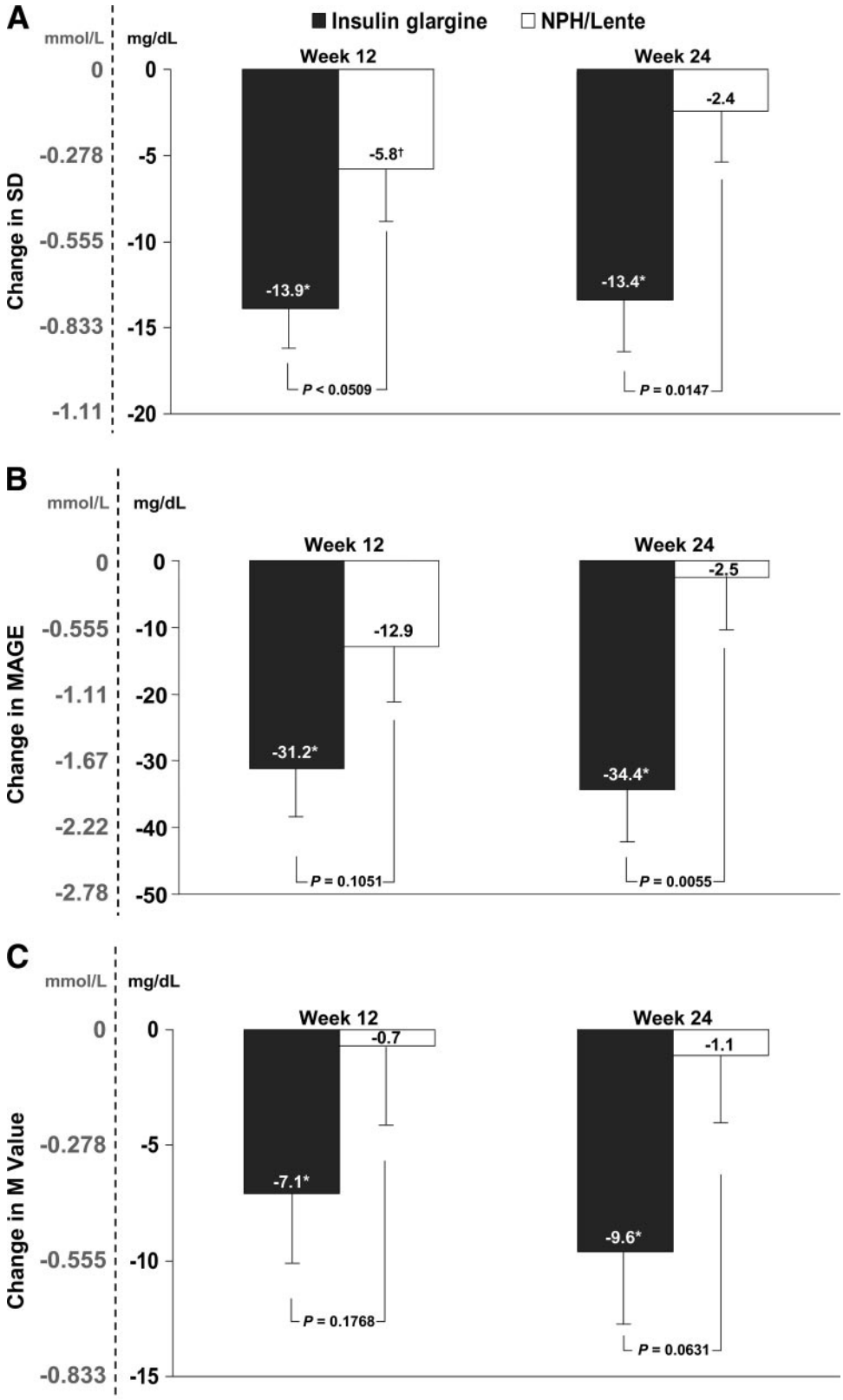

Figure 2—*Adjusted mean change from baseline in measures of glucose variability associated with insulin glargine and intermediate-acting insulin (NPH/Lente).* A*: SD;* *P ≤ *0.05 from baseline;* †P = *0.0503 from baseline.* B*: MAGE;* *P ≤ *0.0001 from baseline.* C*:* M *value;* *P ≤ *0.04 from baseline.*

ences between groups. No other clinical correlates were evaluated.

Although the CGMS subgroup in the current study was similar to the overall study population in terms of demographics, one limitation of this analysis is the possibility that the CGMS subgroup may have been different from the overall population, based on unmeasured variables,

such as motivation, conscientiousness, and other behavioral differences that can affect disease management. Whereas all patients had to have at least Tanner stage 2 pubertal development to enter the study, the impact of different stages of pubertal development on glycemic control and glucose variability could not be determined from the data collected.

In conclusion, the results of this study suggest that the use of insulin glargine as the basal component of a multiple injection regimen appears to be associated with a reduction in glycemic variability. In addition, to the extent to which reduced glycemic variability may contribute to a decrease in diabetes-related complications, the use of insulin glargine may be beneficial.

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