Lower Glucose Variability and Hypoglycemia Measured by Continuous Glucose Monitoring With Novel Long-Acting Insulin LY2605541 Versus Insulin Glargine

Richard M. Bergenstal,[1] Julio Rosenstock,[2] Edward J. Bastyr III,[3] Melvin J. Prince,[3] Yongming Qu,[3] and Scott J. Jacober[3]

CLIN CARE/EDUCATION/NUTRITION/PSYCHOSOCIAL

OBJECTIVE

To use continuous glucose monitoring (CGM) to evaluate the impact of the novel, long-acting basal insulin analog LY2605541 on hypoglycemia and glycemic variability in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Hypoglycemia and glucose variability were assessed with CGM of interstitial glucose (IG) in a subset of patients with type 2 diabetes from a phase II, randomized, open-label, parallel study of LY2605541 (*n* = 51) or insulin glargine (GL) (*n* = 25). CGM was conducted on 3 consecutive days (72–84 h) during the week before week 0, 6, and 12 study visits.

RESULTS

Measured by CGM for 3 days prior to the 12-week visit, fewer LY2605541-treated patients experienced hypoglycemic events overall (50.0 vs. 78.3%, *P* = 0.036) and nocturnally (20.5 vs. 47.8%, *P* = 0.027) and spent less time with IG ≤70 mg/dL than GL-treated patients during the 24-h (25 ± 6 vs. 83 ± 16 min, *P* = 0.012) and nocturnal periods (11 ± 5 vs. 38 ± 13 min, *P* = 0.024). These observations were detected without associated differences in the average duration of individual hypoglycemic episodes (LY2605541 compared with GL 57.2 ± 5.4 vs. 69.9 ± 10.2 min per episode, *P* = NS). Additionally, LY2605541-treated patients had lower within-day glucose SD for both 24-h and nocturnal periods.

CONCLUSIONS

By CGM, LY2605541 treatment compared with GL resulted in fewer patients with hypoglycemic events and less time in the hypoglycemic range and was not associated with protracted hypoglycemia.

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As reliability of technology improves, continuous glucose monitoring (CGM), originally developed as a tool to aid self-management of glycemic control, is increasingly being used as a tool to assess outcomes in diabetes clinical trials (1–3). CGM is particularly useful in studies focusing on hypoglycemia and glycemic variability because it allows for a more comprehensive measurement of time spent in hypoglycemia and hyperglycemia.

[1]International Diabetes Center at Park Nicollet, Minneapolis, MN
[2]Dallas Diabetes and Endocrine Center at Medical City, Dallas, TX
[3]Eli Lilly and Company, Indianapolis, IN

Corresponding author: Scott J. Jacober, jacober_scott_j@lilly.com.

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Hypoglycemia is a major limiting factor for insulin-treated patients in achieving optimal glycemic control (4). In clinical trials, hypoglycemic events are generally captured through patient self-reporting based on signs and symptoms or based on sparse glucose measurements. Therefore, some hypoglycemia events, including nocturnal hypoglycemia events, in the absence of signs and symptoms cannot be effectively captured.

Glycemic variability is an important component of the dysglycemia that characterizes diabetes (5). The relationship of glycemic variability to long-term outcomes remains controversial, but studies have demonstrated that clinical relevance in glycemic variability is greater in patients with diabetes who experience hypoglycemia, in particular severe hypoglycemia (6–10). Consequently, diabetes therapies that can lower glycemic variability may also have the potential to reduce the risk of hypoglycemia and improve quality of life (11).

Longer-acting insulins have been developed to provide more consistent glycemic control during an entire day; however, a potential risk is that the longer duration of action could increase the duration of a hypoglycemic episode. To date, there is no research comparing the duration of individual hypoglycemic episodes between two long-acting insulins in a clinical setting.

The basal insulin analog LY2605541 is a novel, long-acting insulin that consists of insulin lispro modified with a 20-kDa polyethylene glycol moiety that has a large hydrodynamic size, which may slow insulin absorption and reduce renal clearance, resulting in prolonged duration of action (12). Administration of LY2605541 produces a long, flat pharmacodynamic profile with small peak-to-trough fluctuations with a half-life of 2–3 days. LY2605541 demonstrated reduced pharmacokinetic variability, suggesting the potential for less glycemic variability and hypoglycemia (13,14). Therefore, in a predefined substudy in a phase II clinical trial comparing LY2605541 treatment with insulin glargine (GL) in patients with type 2 diabetes, CGM was performed in an investigator-selected cohort of patients to permit a more detailed description of 24-h glycemia, which potentially may include unrecognized hypoglycemia. Use of CGM provides the opportunity to collect comprehensive information on both glycemic control and variability throughout the course of the 24-h day and information on hypoglycemic episodes of which the patient is unaware either from lack of symptoms or sleep. Compared with conventional estimates of hypoglycemia rate and incidence derived from patient self-reporting, additional measures derived from CGM are reported and include the total time spent in hypoglycemia, the mean duration of the hypoglycemic event, and the mean area between the glycemic curve and the glycemic threshold, which provides a composite of the severity of the glucose reduction and its duration. In addition, CGM permits measurement of the duration of individual hypoglycemic events to determine if protracted hypoglycemia is associated with clinical use of a long-acting insulin.

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RESEARCH DESIGN AND METHODS

A detailed description of the study design and results has been previously published (15). In brief, this randomized, open-label, multinational, parallel three-arm, phase II study was conducted to determine if LY2605541 treatment once daily in the morning reduced fasting blood glucose (FBG) by self-monitoring of blood glucose (SMBG) more than similarly administered GL. Patients were randomized 1:1:1 to one of two different LY2605541 insulin-starting and adjusting algorithms or to GL, but as no differences were noted between the two LY arms (13), the data were combined. Eligible patients were aged 18 to 65 years with a diagnosis of type 2 diabetes for at least 1 year, had a hemoglobin A_{1c} (A1C) ≤10.5%, had a BMI between 19 and 45 kg/m^2, and had been using metformin and/or a sulfonylurea in combination with GL or NPH insulin administered once daily (maximum dose <1.0 units/kg/day) for at least 3 months. At enrollment, patients eligible for the main protocol were recruited by investigators to enroll in a protocol substudy that used CGM to evaluate the impact of LY2605541 on glycemic variability and time spent in hypoglycemia compared with GL. Patients were stratified for the addendum and randomized 2:1 (LY2605541:GL), similar to the main protocol. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice and the Declaration of Helsinki. All patients provided written informed consent.

Patients were treated with their assigned basal insulin for 12 weeks after randomization, during which time, the basal insulin dose was optimized with the intent of maintaining the prestudy dose of metformin and/or sulfonylurea. Blinded CGM was performed on 3 consecutive days (72–84 h) during the week before week 0, 6, and 12 study visits. A Medtronic Diabetes (Northridge, CA) CGMS iPro continuous glucose recorder was used. Hypoglycemia for the overall study was defined as an SMBG ≤70 mg/dL (≤3.9 mmol/L) or a sign or symptom associated with hypoglycemia. Nocturnal hypoglycemia for these reported events in the overall study was defined as occurring between sleep and waking and was self-designated by patients. In contrast, the nocturnal period for the CGM assessment was defined as between 2400 and 0600 h.

Hypoglycemia was quantified through various parameters. The time spent in hypoglycemia with interstitial glucose (IG) ≤70 mg/dL and time with IG ≤50 mg/dL were calculated during the 24-h period and during the nocturnal period. The IG area over the curve (AOC) but ≤70 mg/dL (AOC and ≤70) and the IG AOC but ≤50 mg/dL (AOC and ≤50) were calculated to quantify not only the total duration of hypoglycemia but also the severity of hypoglycemia. A hypoglycemic episode was defined as IG ≤3.9 mmol/L (≤70 mg/dL) at any given time point and continuing through until the IG was >3.9 mmol/L (>70 mg/dL) for at least 15 min (or three time points), but these time points with IG >3.9 mmol/L (>70 mg/dL) were not included in the calculation of the duration of the hypoglycemic episode. The Low Blood Glucose Index (LBGI) (16,17), a predictor of severe hypoglycemia, was calculated to quantify both the frequency and severity of hypoglycemia in a nonlinear fashion.

Between- and within-day glucose SD during the nocturnal period and during the daytime period (0600–2400 h) was calculated to assess the within-patient glucose variability. The between-day nocturnal SD was calculated for the SD of daily mean IG between 2400 and 0600 h for each patient visit, and the within-day nocturnal SD was calculated between 2400 and 0600 h for each day for each patient visit and then averaged across the available days for each patient. The between-day daytime SD was calculated for the SD of daily mean glucose between 0600 and 2400 h for each patient visit, and the within-day daytime SD was calculated between 0600 and 2400 h for each day and for each patient visit and then averaged across the available days for each patient. The term "between-day variability" as used in the present article and previously (15) corresponds to what has previously been designated as "standard deviation between daily means" (18,19). The area under the glucose curve (AUC) for the 24-h period was calculated as a measure of overall glycemic exposure.

Statistical Analysis

All analyses were performed using the SAS Drug Development system (SDD; SAS Institute, Cary, NC) with the intent-to-treat principle based on all patients who were randomized and took at least one dose of study drug. All tests performed were two-sided tests at a prespecified α level of 0.1, and the corresponding 90% CIs were calculated, as consistent with the main phase II protocol. No adjustments for multiplicity were performed.

The FBG, AUC, and within- and between-day glucose SDs were analyzed using ANCOVA with variables of treatment group, baseline daily basal insulin dose (≤0.4 and >0.4 units/kg), baseline A1C value (≤8.5 and >8.5%), country, and baseline value of the dependent variable as covariates. The duration and AOC of hypoglycemia were analyzed using ANCOVA with variables of treatment group and baseline value of the dependent variable as covariates. The incidence of hypoglycemia events was compared between treatments using Fisher exact test. The mean duration (in minutes) of individual hypoglycemia episodes by treatment groups at 12 weeks was summarized and compared between treatment groups using Student *t* test.

RESULTS

The characteristics of the CGM and complete study cohorts are presented in Table 1. During the 12 weeks of treatment, the rate (per patient per 30 days) of patient-reported total hypoglycemia for the CGM cohort was similar between LY2605541 and GL treatments (LY2605541, 2.01; GL, 2.77; *P* = 0.21), but the rate of patient-reported nocturnal hypoglycemia was less for LY2605541-treated patients (LY2605541, 0.45; GL, 0.60; *P* = 0.08). The incidence of total and nocturnal

Table 1—Characteristics of CGM and complete cohorts

	LY2605541		GL			
	Complete cohort (*n* = 195)	CGM cohort (*n* = 51)	Complete cohort (*n* = 93)	CGM cohort (*n* = 25)	Complete cohort *P* value	CGM cohort *P* value
Baseline						
Age (years)	59 ± 10	60 ± 9	61 ± 8	60 ± 9	0.110	0.896
Male, *n* (%)	106 (54.4)	32 (62.7)	47 (50.5)	15 (60.0)	0.614	1.000
Caucasian, *n* (%)	181 (92.8)	44 (86.3)	87 (93.5)	22 (88.0)	0.101	1.000
Duration of disease (years)	11.8 ± 7.4	12.2 ± 7.1	12.1 ± 6.9	13.1 ± 8.0	0.760	0.623
Body weight (kg)	90.7 ± 19.1	96.8 ± 20.8	89.7 ± 20.1	91.0 ± 20.1	0.845	0.247
BMI (kg/m^2)	31.9 ± 5.1	33.0 ± 5.6	32.3 ± 5.2	32.5 ± 6.1	0.529	0.764
A1C (%)	7.74 ± 1.08	7.69 ± 1.11	7.83 ± 1.08	7.70 ± 1.05	0.766	0.964
Daily mean BG by SMBG (mg/dL)	170 ± 40	170 ± 41	165 ± 35	164 ± 36	0.073	0.215
24-h glucose AUC (mg/dL*min) [mean glucose, mg/dL]	—	238,140 ± 59,838 [165 ± 42]	—	224,491 ± 53,803 [156 ± 37]	—	0.155
FBG by SMBG (mg/dL)	147 ± 40	143 ± 41	140 ± 39	134 ± 36	0.131	0.370
FBG by central laboratory (mg/dL)	146 ± 42	141 ± 38	151 ± 46	136 ± 44	0.404	0.687
Week 12						
A1C (%)	6.97 ± 0.75	6.97 ± 0.79	7.16 ± 0.81	6.97 ± 0.79	0.279	0.644
Daily mean BG by SMBG (mg/dL)	139 ± 27	150 ± 29	145 ± 30	150 ± 35	0.741	0.500
24-h glucose AUC (mg/dL*min) [mean glucose, mg/dL]	—	214,083 ± 44,751 [149 ± 31]	—	205,322 ± 46,505 [143 ± 32]	—	0.172
FBG by SMBG (mg/dL)	118 ± 27	126 ± 30	117 ± 25	112 ± 19	0.433	0.078
FBG by central laboratory (mg/dL)	123 ± 36	120 ± 37	129 ± 38	125 ± 47	0.347	0.672

Data are mean ± SD. BG, blood glucose.

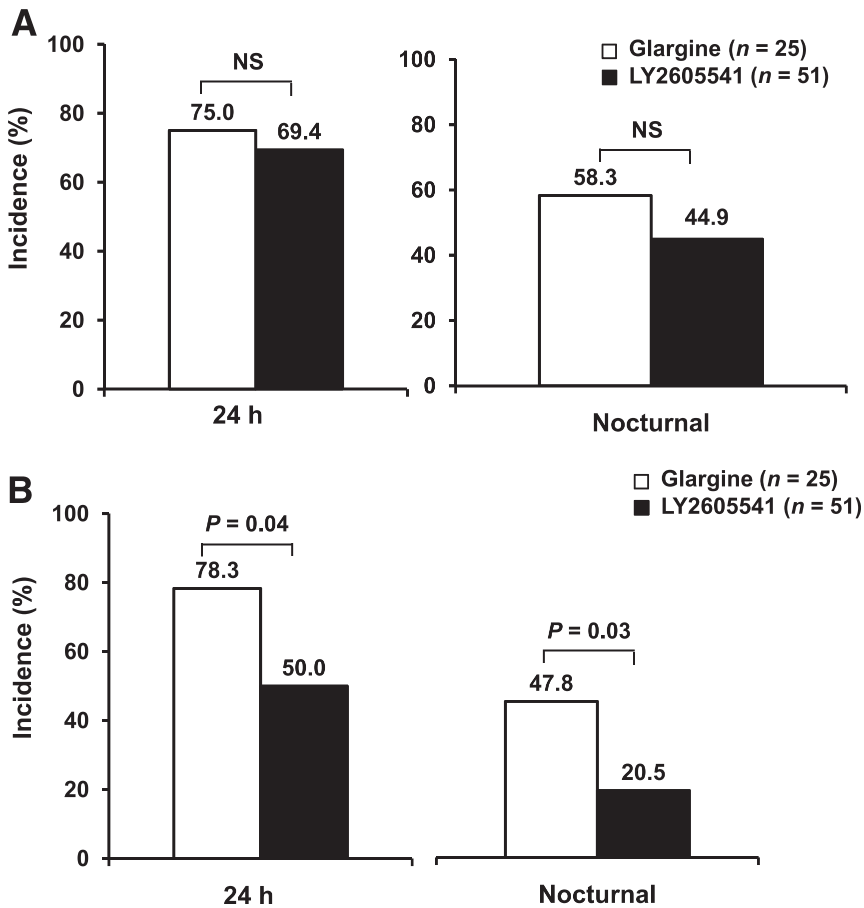

Figure 1—*A*: Hypoglycemia incidence for patient-reported total and nocturnal hypoglycemia as measured by SMBG. *B*: Hypoglycemia incidence for total and nocturnal hypoglycemia as measured by CGM. NS, not significant.

hypoglycemia based on patient self-reporting was not significantly different between LY2605541 and GL (Fig. 1*A*). The incidence of hypoglycemia via CGM during the 3 days prior to week 12 during the 24-h and nocturnal periods was statistically significantly lower in LY2605541- than GL-treated patients (Fig. 1*B*).

At week 12, as measured by CGM, LY2605541-treated patients spent statistically significantly less time with IG ≤70 and ≤50 mg/dL than GL-treated patients during the 24-h (Fig. 2*A*) and nocturnal periods (Fig. 2*B*). On average, the duration of a hypoglycemic event was similar between LY2605541- and GL-treated patients (Fig. 2*C*). Mean AOC and ≤70 mg/dL and mean AOC and ≤50 mg/dL at 12 weeks were statistically significantly lower in LY2605541- than GL-treated patients (Fig. 2*D*). The LBGI, a predictor of severe hypoglycemia, was statistically significantly lower in LY2605541-treated patients compared with GL-treated patients during both the 24-h (LY2605541, 0.6 ± 0.1; GL, 1.6 ± 0.3; P = 0.01) and nocturnal periods (LY2605541, 0.9 ± 0.3; GL, 2.7 ± 0.7; P = 0.01).

Daytime and nocturnal within-day glucose variabilities at week 12 were statistically significantly lower in LY2605541-treated patients compared with GL-treated patients (Fig. 3). In contrast, there was no statistically significant difference in 24-h (LY2605541, 10.1 ± 0.9 mg/dL; GL, 17.3 ± 3.8 mg/dL; P = 0.11) and nocturnal (LY2605541, 18.7 ± 2.2 mg/dL; GL, 19.3 ± 3.4 mg/dL; P = 0.91) between-day glucose variability (SD) at week 12 in LY2605541-treated patients compared with GL-treated patients.

CONCLUSIONS

This study in a CGM cohort from a phase II, randomized, open-label, parallel study, comparing LY2605541 with GL, demonstrated that treatment with the novel, long-acting basal insulin LY2605541 in patients with type 2 diabetes resulted in less time spent in hypoglycemia, a lesser severity of hypoglycemia, and a reduced risk of severe hypoglycemia as measured by the LBGI. Furthermore, the hypoglycemic events with LY2605541 treatment were not protracted compared with GL, as indicated by the similar mean duration of hypoglycemic episodes, which can only be derived from CGM. These differences were noted despite the fact that LY2605541 and GL resulted in similarly improved overall glycemic control as measured by A1C and FBG. The CGM-based hypoglycemia data from this cohort substantiate the overall study results despite different observational methods.

The LBGI was developed to quantitate both the frequency and severity of hypoglycemia, has been validated

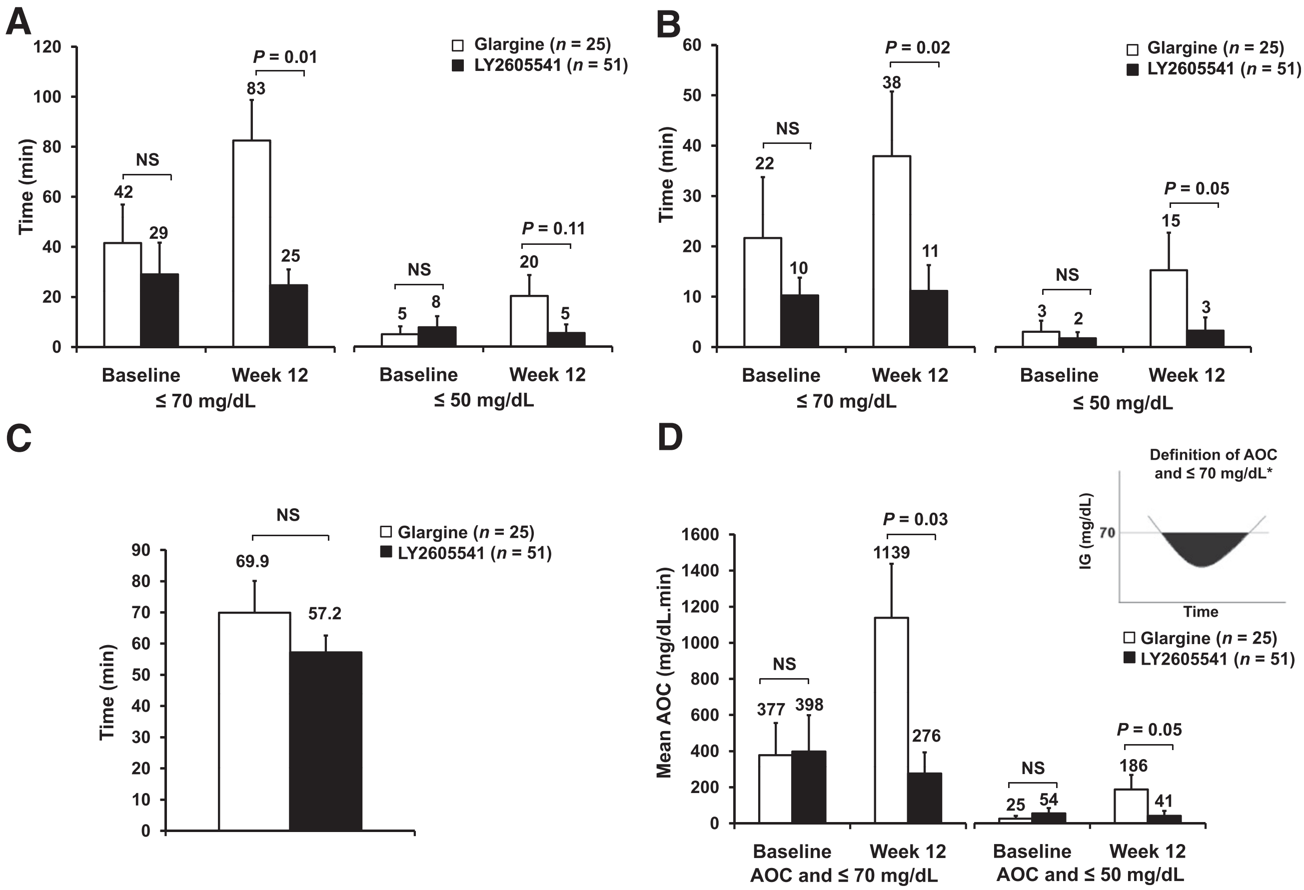

Figure 2—*A*: Time spent in hypoglycemia (≤70 and ≤50 mg/dL) over 24 h at baseline and week 12. *B*: Time spent in nocturnal hypoglycemia (≤70 and ≤50 mg/dL) at baseline and week 12. *C*: Mean duration of a hypoglycemic event at week 12. *D*: Mean AOC and ≤70 and ≤50 mg/dL over 24 h (the mean duration of a hypoglycemic event and the mean area between the glycemic curve and the hypoglycemic threshold). NS, not significant. *Hypoglycemia: IG ≤70 mg/dL and continued until IG >70 mg/dL for 15 min (or three time points).

as a predictor of severe hypoglycemia (16,17), and also has a high sensitivity to changes in glycemic profiles and control (20). Although no severe hypoglycemia was observed in this study, which was only 12 weeks in duration, LBGI results demonstrated that LY2605541-treated patients would be at a statistically significantly lower risk for severe hypoglycemia. The AOC and ≤70 mg/dL and the AOC and ≤50 mg/dL, which are also measures of the severity of hypoglycemic events, characterize both the duration of the event and the magnitude of the hypoglycemic blood glucose value over time. These measures for LY2605541 were also less than those for GL and were also consistent with the LBGI, again suggesting a decreased risk for hypoglycemia with LY2605541. These data are preliminarily, but not conclusively, reassuring that a basal insulin with a notably longer half-life (14) does not increase the risk (LBGI), severity (AOC and ≤70 mg/dL), or duration of hypoglycemia in patients with type 2 diabetes.

The observations of reduced glycemic variability with the CGM data are also consistent with the SMBG profiles of the clinical trial (15). The reduced glycemic variability may be hypothesized to result from the prolonged duration of action and flat profile previously demonstrated with LY2605541 compared with GL (13).

The strengths of this research include the following. Although CGM was not collected in all patients, a subset of 76 patients participated in the CGM procedure, accounting for >25% of the total cohort. The continuous monitoring of glucose values facilitates a more comprehensive assessment of hypoglycemia and its risk, such as time in the hypoglycemic range, the duration of individual hypoglycemic episodes, AOC and ≤70 mg/dL (a composite of duration and severity of hypoglycemia), and LBGI (a predictor of severe hypoglycemia). CGM may potentially provide a more detailed assessment of hypoglycemia, especially nocturnal, as patient-reported hypoglycemic events may not be fully captured. The CGM monitoring in this study also provides less biased data as both patient and investigator are blinded to the results.

The limitations of our study conclusions include those related to CGM technology. CGM has been described as being significantly lower in accuracy than SMBG, especially at hypoglycemic levels (21). Although CGM provides a more detailed description of 24-h glycemia and greater opportunity to detect unrecognized hypoglycemia (22–25) than routine SMBG, none of these studies used an alternative

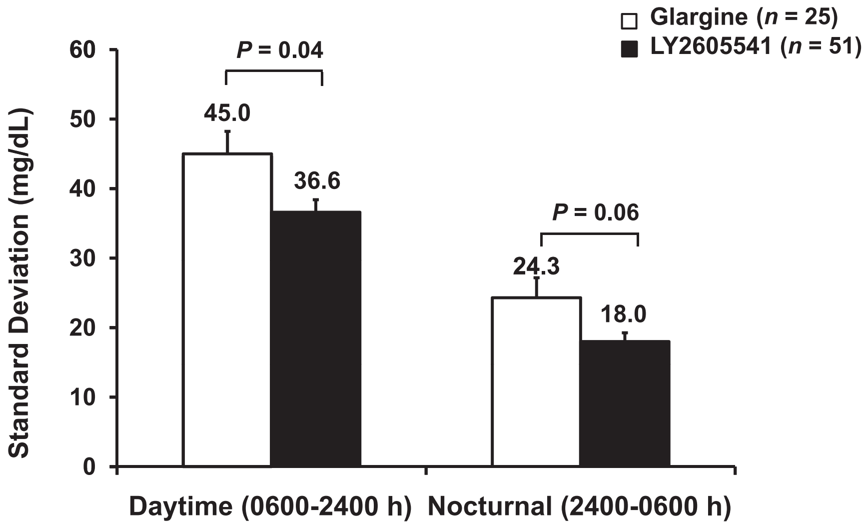

Figure 3—Within-day glucose variability at week 12.

method to confirm the undetected hypoglycemia events identified by CGM, and therefore, these studies may have overreported or underreported hypoglycemia. Of note, the CGM data were only collected during a 3-day interval in contrast to the 12 weeks of patient self-reported hypoglycemia data that was collected during the course of the trial. Therefore, these observations may be less representative of a much longer period of observation. Despite these potential limitations, the conclusions from the CGM data in this study are consistent with and confirm and extend the SMBG findings of the complete patient cohort in the clinical trial. Additionally, the CGM system used in this trial has been reported to provide readings that are in good agreement with SMBG (26). Finally, this study is further limited by its open-label design, small number of participants, and the fact that patients were enrolled by investigator selection and not randomized to the substudy.

This phase II substudy was exploratory by definition, and therefore confirmation by phase III studies is required for more conclusive results. In conclusion, the comprehensive evaluation by CGM in this limited patient cohort substantiates and extends the hypoglycemia and glycemic variability findings derived from SMBG of the complete patient cohort in the clinical trial. LY2605541 treatment compared with GL treatment resulted in fewer patients experiencing hypoglycemia and less time spent in hypoglycemia. Notably, this longer-acting basal insulin did not appear to be associated with protracted hypoglycemia, an increase in the severity of hypoglycemia, or an increase in the risk of hypoglycemia compared with GL.

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