Lowest Glucose Variability and Hypoglycemia Are Observed With the Combination of a GLP-1 Receptor Agonist and Basal Insulin (VARIATION Study)

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OBJECTIVE

There is a dearth of published literature comparing glucose variability (GV) between different insulin regimens in type 2 diabetes. This cohort study compares GV using continuous glucose monitoring (CGM) in patients with well-controlled type 2 diabetes using four common insulin regimens: basal insulin + oral drugs (BO), basal insulin + glucagon-like peptide 1 receptor agonist (GLP-1 RA) (BGLP), premixed insulin (PM), and basal-bolus insulin (BB).

RESEARCH DESIGN AND METHODS

Consecutive patients from three endocrinology clinics who met study criteria—type 2 diabetes, age 18 to 80 years, BMI ≤ 45 kg/m^2, stable insulin regimen for a minimum of 6 months, and stable A1C value ≤7.5% (58 mmol/mol) before study enrollment—underwent 6-day masked CGM. Hypoglycemia was defined as a sensor glucose concentration <70 mg/dL on CGM.

RESULTS

A total of 160 patients with comparable baseline characteristics formed four equal insulin regimen cohorts. The daily glucose SD (the primary outcome) was significantly lower in the BGLP cohort versus the BO, PM, and BB cohorts ($P = 0.03$, $P = 0.01$, and $P < 0.01$, respectively), and remained so after adjusting for age, BMI, type 2 diabetes duration, and A1C. Similarly, daily hypoglycemia outcomes on CGM were least for the BGLP cohort.

CONCLUSIONS

The lowest GV and lowest hypoglycemia were observed in patients using the combination of basal insulin with a GLP-1 RA, supporting the complementary glycemic action of these agents in type 2 diabetes. These observed benefits in GV and hypoglycemia may contribute to the cardiovascular outcome reduction seen with GLP-1 RA therapy and should be investigated further.

Type 2 diabetes is a chronic and progressive disease associated with multiple complications. The duration of type 2 diabetes and the degree of glycemic control are major risk factors for microvascular and macrovascular complications (1). Insulin therapy is often required to achieve optimal glycemic control in patients with type 2 diabetes, but it is also often associated with adverse effects such as hypoglycemia and weight gain (2).

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The majority of intervention trials in type 2 diabetes to date have focused on A1C as the primary measure of glycemic control. Secondary outcomes in these trials have included self-reported hypoglycemia based on self-monitored blood glucose (SMBG), which itself may be considered less reliable than continuous glucose monitoring (CGM) for total hypoglycemic episodes and multiple other aspects of glycemic variability (GV). GV is possibly related to the pathogenesis of diabetes complications (3–6). In addition, hypoglycemia may be implicated in adverse clinical outcomes based on post hoc analysis of large, randomized clinical trials targeting intensive glycemic control, though whether this simply represents risk prediction in contrast to causal association has been debatable (7). Finally, lower GV may also reduce patients' need for frequent self-monitoring and aid in the achievement of glycemic control goals (8).

Incretin agents are known to have a low associated risk of hypoglycemia because of their glucose-sensitive mechanisms of insulin release and glucagon suppression (9,10). Glucagon-like peptide 1 (GLP-1) receptor agonists (RAs) in particular also have effects on gastric motility and satiety that provide significant benefits for postprandial glycemic excursions (11). Hence, it is plausible that GLP-1 RAs may be associated with less GV and hypoglycemia when combined with basal insulin. Studies based on SMBG assessments suggest improved GV with the addition of a GLP-1 RA to basal glargine insulin (12,13). Even though a reduction of self-reported daytime hypoglycemia on SMBG was observed in one randomized controlled trial with exenatide + basal glargine insulin versus a basal bolus insulin regimen (14), another recent randomized controlled trial that randomized patients to the same insulin regimens did not find a significant reduction in hypoglycemia end points on CGM measurements, though GV was modestly reduced (15).

The objective of the Variability of Glucose in Patients with Type 2 Diabetes Treated with Four Different Insulin Combination Regimens (VARIATION) study was to determine whether patients with type 2 diabetes who had good, stable glycemic control (A1C $\leq$7.5% [58 mmol/mol]) on a basal insulin + GLP-1 RA regimen demonstrate less GV and hypoglycemia compared with three other common insulin management strategies.

RESEARCH DESIGN AND METHODS

In the prospective VARIATION cohort study, consecutive patients attending three large, community-based, multidisciplinary endocrinology clinics between November 2013 and December 2014 were recruited sequentially if they met the study criteria. All subjects provided written informed consent before any study procedures. They underwent masked CGM using the iPro2 device (Medtronic, Northridge, CA) over a 6-day period. The VARIATION study was funded independently by LMC Diabetes & Endocrinology, with no external funding source. This study was carried out in accordance with the principles of the Declaration of Helsinki (2004 version) and the requirements of Good Clinical Practice guidelines and was approved by the local ethics committee.

Study Design

Consecutive patients from the three clinic sites who achieved good glycemic control (defined as A1C $\leq$7.5% [58 mmol/mol]) using any of the four prespecified insulin combination regimens were invited to participate. A total of 160 subjects formed four equal cohorts of 40 patients each, based on their insulin therapy regimen: *1*) a basal + oral (BO) regimen (long-acting insulin in combination with one or more oral antidiabetic agent [OAD]); *2*) a basal + GLP-1 RA (BGLP) regimen (long-acting insulin in combination with a GLP-1 RA [exenatide or liraglutide] $\pm$ an OAD); *3*) a premixed insulin (PM) regimen (two or more premixed insulin injections per day $\pm$ an OAD); or *4*) a basal bolus insulin (BB) regimen (three or more bolus insulin injections and one or more long-acting insulin injection per day $\pm$ an OAD).

The inclusion criteria for the VARIATION study were type 2 diabetes; age between 18 and 80 years (inclusive); stable health and dietary regimen; BMI $\leq$45 kg/m^2; good glycemic control (A1C documented with a value $\leq$7.5% [58 mmol/mol] within the previous 3 months); a minimum long-acting insulin dose of $\geq$10 U/day with stable total insulin doses ($\pm$10% of the current dose) and regimen for a minimum of 6 months; and an additional OAD and/or GLP-1 RA at stable doses for a minimum of 3 months. Permitted OADs were metformin, sulfonylureas (excluding glyburide), meglitinide, acarbose, and a dipeptidyl peptidase 4 inhibitor. Exclusion criteria were type 1 diabetes; estimated glomerular filtration rate $<$40 mL/min or measured serum creatinine concentration $>$2 mg/dL within the 3 months before study enrollment; enrollment in an intensive weight loss program; history of severe gastroparesis; severe hypoglycemic reaction (defined as third-party or ambulance assistance or emergency department visit) within the prior 3 months; or treatment with a GLP-1 RA in any cohort other than the BGLP group.

CGM Data Collection

Eligible individuals who agreed to participate and signed an informed consent document were monitored by a masked CGM for a continuous 6-day period without a change in their diabetes regimen. Patients were encouraged to record four SMGB (capillary blood) levels each day to calibrate the CGM, and to record meal times, exercise, missed medications, and symptoms of hypoglycemia. They were instructed to follow their usual diet and exercise regimen and were advised to abstain from intense and prolonged exercise, eating binges, and alcohol during the 6-day period. The CGM values were considered valid only if the monitor was worn for the full 6-day period, with good-quality data recording, and if the subject reported adherence to usual diet and medications and did not suffer any significant intercurrent illness. A decision to repeat the CGM was to be made at the disconnection visit before downloading data if the above criteria were not met; such subjects who agreed to repeat the CGM were assigned a new study enrollment number. To minimize ascertainment bias, designated research staff members downloaded the CGM data and were blinded to cohort assignment and study objective, while a separate research associate was responsible for patient assessments and data collection. Once 40 completed and valid CGM records were obtained, enrollment into each cohort was halted.

Study Outcomes

Patients' baseline characteristics were summarized by cohort. Continuous and categorical variables were reported as mean (SD) and number (percentage), respectively. The primary outcome was the average daily glucose SD over the

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measurement days, as measured by the device. SD was chosen because of its general familiarity and validation history in quantifying GV from CGM (16,17), especially in our setting where two contributing variables, A1C and mean glucose, were expected to be controlled among all four cohorts. In addition, the secondary outcomes in our study included total glucose SD, daily average glucose, daily frequency of hypoglycemia, daily percentage of time of hypoglycemia, daily duration (in minutes) of hypoglycemia, daily frequency of hyperglycemia, daily percentage of time of hyperglycemia, and area under the curve (AUC) for hyperglycemia.

The total SD was calculated by the device for the overall measurement period. Daily average glucose was calculated by averaging the daily mean glucose as measured by the device. The frequency of hypoglycemia was calculated as the average number of daily episodes of hypoglycemia (glucose concentration below the threshold of 70.2 mg/dL, as measured by the device).

The duration of hypoglycemia was calculated as the average daily percentage of time where the glucose concentration, as measured by the device, was below the glycemic threshold. The daily duration of hypoglycemia in minutes (as an average over the measurement days) was also reported. The degree of hypoglycemia was calculated as the mean daily AUC where the glucose concentration was outside of the normal range as measured by the device. The frequency of hyperglycemia, the duration of hyperglycemia, and the degree of hyperglycemia are calculated similarly for a glucose concentration above a threshold of 180 mg/dL, as measured by the device.

Sample Size Calculation

From the analysis of a large database of patients with diabetes within the LMC clinics, we observed that daily GV for controlled patients was approximately 36 mg/dL, with an SD of 18 mg/dL. Among the four cohorts, we further assumed that the smallest mean daily glycemic variability was at most 27 mg/dL, and the largest mean daily variability was at least 45 mg/dL; the remaining two cohorts had a mean daily variability of 36 mg/dL. To detect such magnitude of difference among groups using an *F* test with a 5% α level, 30 patients were needed per cohort (assuming an equal size per cohort) to achieve 90% power. After adjusting for a total of 4 covariates (with 10 patients each), the total sample size required was 160.

Statistical Methods

Sample size was calculated in G*Power version 3.1.2. All statistical analyses were performed in SAS 9.2 and SPSS 19.0. For continuous outcomes that follow an approximate normal distribution, the ANCOVA model was used to test whether at least one cohort was significantly different from the rest by adjusting for age, BMI, baseline A1C, and diabetes duration. A quartile-quartile plot was used to examine the normality assumption. For continuous outcomes that did not follow an approximate normal distribution, a nonparametric ANCOVA model was used. The α level was set at 5%. If a significant difference existed between cohorts, multiple pairwise comparisons would be performed to explore which pairs differed.

RESULTS

A total of 187 subjects were enrolled, whereas 27 subjects were excluded from the study for the following reasons: 11 had problems relating to the completion of CGM recording; 7 experienced medication instability or nonadherence; 5 had an unexpected change in baseline diet or exercise during the CGM period; and 4 subjects had acute medical conditions arise during the 6-day study period. Hence, 160 patients with comparable baseline characteristics, including age, BMI, duration of diabetes, and prior diabetes education (Table 1), made up the four equal cohorts. Documented histories of microvascular (neuropathy, retinopathy, and nephropathy) and macrovascular (myocardial infarction, coronary artery disease, stroke, and peripheral vascular disease) complications were not statistically different among the four cohorts (proportion of microvascular complications ranged from 40% in the BGLP cohort to 50% in the BB cohort; the proportion of macrovascular complications ranged from 17.5% in the BO cohort to 32.5% in the PM cohort). Among subjects, 87% were using metformin, while analog long-acting insulin was prescribed for 100% of subjects (88 taking glargine and 32 taking detemir), excluding the PM cohort. Within the BGLP cohort, liraglutide was the prescribed GLP-1 RA for 39 subjects, while 1 subject was taking exenatide twice daily. None of the enrolled subjects were using potentially confounding therapies such as corticosteroids; β-blockers were prescribed in a minority of patients among the four cohorts (BO group, 30%; BGLP group, 20%; PM group, 46%; BB group, 22%; $P = 0.05$, overall difference). No adverse events relating to study procedures were reported during the 6-day CGM period.

Continuous Glucose Monitoring

The primary end point results of daily glucose SD ($P = 0.01$ in ANCOVA modeling adjusting for age, BMI, diabetes duration, and baseline A1C) as well as additional SD measurements are shown in Table 2. Comparison between cohorts showed that the daily glucose SD in the BGLP cohort (30.6 $\pm$ 9 mg/dL) was significantly lower than that of the other cohorts: BO, 34.2 $\pm$ 9 mg/dL; PM, 36 $\pm$ 10.8 mg/dL; and BB, 37.8 $\pm$ 9 mg/dL. Total SD was also significant in the ANCOVA

Table 1—Baseline characteristics of the four insulin regimen cohorts

	Cohorts			
	BO (n = 40)	BGLP (n = 40)	PM (n = 40)	BB (n = 40)
Male sex	58%	60%	65%	60%
Age (years)	64 (10)	59 (9)	65 (10)	63 (9)
A1C before study (%)	6.9 (0.4)	6.9 (0.4)	7.0 (0.5)	7.0 (0.4)
A1C before study (mmol/mol)	52 (4)	52 (4)	53 (5)	53 (4)
Diabetes duration (years)	16 (8)	15 (8)	19 (8)	17 (8)
BMI (kg/m^2)	31 (6)	32 (5)	30 (5)	32 (5)
Waist circumference (cm)	104 (13)	109 (13)	104 (10)	107 (11)
Estimated glomerular filtration rate (mL/min/1.73 m^2)	74 (19)	79 (22)	70 (23)	71 (24)
Prior diabetes education	90%	83%	78%	83%

Data are presented as mean (SD) unless otherwise indicated.

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adjustment model, with the lowest value, 34.2 ± 1.08 mg/dL, observed in the BGLP cohort, compared with 39.6 ± 10.8, 41.4 ± 10.8, and 43.2 ± 10.8 mg/dL for the BO, PM, and BB cohorts, respectively. Similarly, the daily SD by average glucose for the BGLP cohort trended lower when compared individually with the BO, PM, and BB cohorts ($P = 0.07$, $P = 0.06$, and $P = 0.05$, respectively), even though this was not statistically significant in the ANCOVA models.

Hypoglycemia end points were also statistically significantly different among the cohorts and remained so even after adjusting for age, BMI, diabetes duration, and baseline A1C (Table 2). Importantly, the time in hypoglycemia was lowest in the BGLP cohort at a median of 2.9 min/day (interquartile range [IQR] = 25.7) followed by the BO (7.3 min/day; IQR = 35.0), PM (23.6 min/day; IQR = 35.7), and BB (31.1 min/day; IQR = 67.0) cohorts.

Among the hyperglycemia outcomes, the daily AUC above the threshold for hyperglycemia was significantly lower in the BGLP cohort (median, 0.1; IQR = 0.3) when compared separately with the PM (median, 0.3; IQR = 0.4; $P = 0.01$) and BB (median, 0.3; IQR = 0.4; $P < 0.01$) cohorts. However, all the other hyperglycemia outcomes measured were not significantly different among the cohorts in the ANCOVA model adjusting for age, BMI, diabetes duration, and baseline A1C.

Self-reported Hypoglycemia Incidence on SMBG

Total self-reported hypoglycemia incidences on SMBG during the 6-day CGM period were statistically significant in ANCOVA models adjusting for age, BMI, diabetes duration, and baseline A1C ($P < 0.01$); this incidence was highest for the BB cohort ($P < 0.01$ vs. the BGLP cohort; $P < 0.01$ vs. the BO cohort; $P = 0.03$ vs. the PM cohort). In addition, the BGLP cohort had a lower incidence of self-reported hypoglycemia compared with the PM cohort ($P = 0.05$). Figure 1 depicts the proportion of patients with at least one self-reported hypoglycemia incident during the 6-day study period, with higher incidence reported for the BB cohort compared with the BO and BGLP cohorts ($P < 0.01$). In addition, the BB cohort had a numerically higher proportion of one or more

Table 2—ANCOVA and direct cohort comparisons for primary and secondary outcomes from 6-day CGM data

	Cohorts					
	BO	BGLP	PM	BB	*P* value^	Between-cohort comparisons
Glucose (mg/dL)						
Daily SD (primary outcome)*	34.2 (9)	30.6 (9)	36.0 (10.8)	37.8 (9)	0.01	BGLP vs. PM ($P = 0.01$) BGLP vs. BB ($P < 0.01$) BO vs. BGLP ($P = 0.03$)
Total SD*	39.6 (10.8)	34.2 (10.8)	41.4 (10.8)	43.2 (10.8)	0.01	BGLP vs. PM ($P = 0.01$) BGLP vs. BB ($P < 0.01$) BO vs. BGLP ($P = 0.04$)
Daily average*	136.8 (19.8)	138.6 (21.6)	144 (19.8)	142.2 (23.4)	0.74	
Daily SD by average*	19.8 (10.8)	16.2 (7.2)	19.8 (9)	19.8 (10.8)	0.20	BGLP vs. PM ($P = 0.06$) BGLP vs. BB ($P = 0.05$) BO vs. BGLP ($P = 0.07$)
Hypoglycemia						
Daily frequency**	0.1 (0.4)	0.1 (0.4)	0.4 (0.7)	0.3 (0.4)	0.02	BGLP vs. PM ($P = 0.02$) BGLP vs. BB ($P = 0.01$)
Daily percentage of time**	0.6 (3.6)	0.1 (2.1)	1.9 (3.9)	2.5 (4.5)	0.02	BGLP vs. PM ($P = 0.02$) BGLP vs. BB ($P < 0.01$)
Daily duration (min)**	7.3 (35.0)	2.9 (25.7)	23.6 (35.7)	31.1 (67.0)	0.01	BGLP vs. PM ($P = 0.03$) BGLP vs. BB ($P < 0.01$)
Hyperglycemia						
Daily frequency*	1.8 (0.9)	1.7 (1.0)	1.8 (0.8)	1.8 (0.8)	0.85	
Daily percentage of time*	16.4 (12.9)	14.5 (13.7)	20.2 (13.1)	20.4 (12.9)	0.26	
AUC**	0.2 (0.5)	0.1 (0.3)	0.3 (0.4)	0.3 (0.4)	0.04	BGLP vs. PM ($P = 0.01$) BGLP vs. BB ($P < 0.01$)

^Adjusted for age, BMI, diabetes duration, and baseline A1C. *Data are presented as mean (SD). **Data are presented as median (IQR). All *P* values <0.1 (close to significance) are presented.

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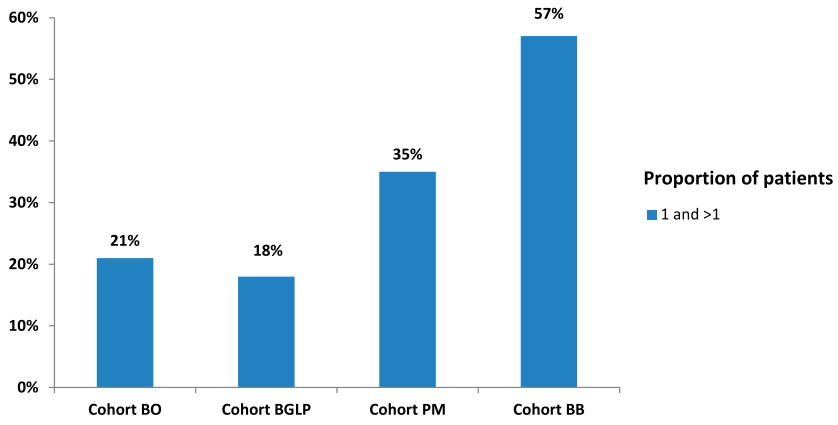

Figure 1—Proportion of patients with at least 1 reported hypoglycemia event during self-monitoring within the 6-day study period. $P < 0.01$, BB cohort vs. BO and BGLP cohorts.

than one hypoglycemia incident reported compared with the PM cohort, but this did not reach statistical significance ($P = 0.07$). No episodes of severe hypoglycemia (i.e., requiring medical assistance) were reported for any study patient.

CONCLUSIONS

In the VARIATION cohort study, which examined patients with type 2 diabetes mellitus achieving good mean glucose control, the lowest GV was observed among subjects receiving a combination of long-acting basal insulin with a GLP-1 RA compared with three other common insulin therapy regimens. Indeed, all 3 measures of SD (including daily glucose SD, a primary outcome) favored the BGLP cohort compared with the other 3 insulin regimens, even after adjusting for potential confounding variables of age, BMI, diabetes duration, and A1C. A second important finding from our study is that for hypoglycemia, whether measured by frequency, duration, or daily percentage of time, the most favorable results were also consistently observed among the BGLP cohort compared with the PM and BB cohorts. The BO cohort also had numerically higher hypoglycemia parameters on CGM and SMBG compared with the BGLP cohort, though these did not reach statistical significance.

The complementary mechanisms of the combination of GLP-1 RA and basal insulin, addressing both postprandial as well as fasting hyperglycemia (18), likely resulted in lower GV for this combination in our study. GLP-1 RAs are known to stimulate insulin secretion and inhibit glucagon secretion in the setting of hyperglycemia in a glucose-sensitive manner (8,9). At the same time, hypoglycemic counter-regulatory processes are maintained (19,20). The improved hypoglycemia outcomes among the BGLP cohort in the VARIATION study are supported by studies that have shown a neutral to potentially protective role for GLP-1 RAs during insulin-induced hypoglycemia. Glucagon and other counter-regulatory responses were preserved with GLP-1 RA versus placebo in healthy volunteers subjected to a hypoglycemic clamp (19). In patients with type 1 diabetes, glucagon responsiveness to hypoglycemia was preserved with liraglutide. In fact, in this crossover trial, lower glucose infusion rates were required during the clamp for all three liraglutide doses compared with placebo (20). This finding has led to speculation that the reduced need for exogenous glucose during experimental hypoglycemia might predict reduced severity of hypoglycemic events during liraglutide treatment in the clinical setting.

GV, acute hyperglycemia and hypoglycemia may have potential clinical implications because of their postulated associations with complex vascular endothelial effects, including activation of prothrombotic, proinflammatory, and proatherogenic mechanisms as well as oxidative stress (21–26). Oxidative stress and endothelial dysfunction may in turn link GV and hypoglycemia to vascular complications in diabetes. As an alternate mechanism associating hypoglycemia to cardiac outcomes, Chow et al. (27) observed that hypoglycemia was associated with cardiac arrhythmias among older patients with type 2 diabetes treated with insulin. Similarly, in a post hoc analysis of the ORIGIN trial with basal glargine insulin, severe hypoglycemia was noted to increase the risk of arrhythmia-related death by 77% (28). Unfortunately, few other published data examine the direct effects of hypoglycemia on arrhythmias among patients in an outpatient research setting.

Accumulating in vitro and clinical evidence suggests a beneficial cardiovascular (CV) role for GLP-1 RA therapies in diabetes, with a potential link via their impact on GV or hypoglycemia risk. GLP-1 administration has been shown to counterbalance the deleterious effects of hyperglycemia or hypoglycemia on endothelial dysfunction, oxidative stress, and inflammation in people with type 1 diabetes (29). Moreover, a series of clamp experiments have suggested that the combination of insulin and GLP-1 is more effective than either alone in improving endothelial dysfunction, inflammation, and oxidative stress in type 2 diabetes (30). In addition, GLP-1 may help preserve myocardial glucose uptake during hypoglycemia in insulin-resistant healthy men (31). The LEADER CV outcome trial (CVOT) (32) recently found significantly reduced CV-related death and a lower risk of severe hypoglycemia with the GLP-1 RA liraglutide compared with nonincretin therapies. Although not directly comparable, the intensive treatment arm of the ACCORD trial showed an increase in CV-related mortality, despite reduced myocardial infarction. Although hypoglycemia does not provide a direct explanation for this higher mortality, reported incidence in the ACCORD trial likely under-represents the true extent of hypoglycemia, which is optimally assessed using technology such as CGM (33). A large CVOT with the dual aim of achieving target A1C and minimizing both GV and hypoglycemia may ideally illustrate the potential of optimal glycemic control to reduce CV event risk. The feasibility of such a CVOT using a combination of basal insulin + GLP-1 RAs is supported by the pilot FLAT SUGAR trial, which compared this combination to a basal bolus insulin approach in a randomized fashion (15). In addition, it is hoped that further analysis from LEADER, SUSTAIN-6 (34), and future CVOTs of other GLP-1 RA therapies

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(35,36) could help determine the impact of these combination therapies on CV events in patients with type 2 diabetes.

The observational cohort design of VARIATION may be considered a study limitation. Nonetheless, the following specifics of the study protocol likely improve the validity of our results while minimizing confounding and bias: *1*) We invited consecutive patients attending their regular diabetes clinic visits to participate in the study. *2*) Enrolled participants had a high level of diabetes education attendance across the study cohorts. *3*) We masked the patients to the CGM results over the 6-day recording. *4*) We designated one research staff, blinded to cohort assignment and study objectives, to download the CGM data, while a separate research associate was responsible for patient assessment and data collection. *5*) We adjusted both the CGM-based SD and hypoglycemia end points for age, BMI, diabetes duration, and A1C. Other than the adjustment for these four variables, potential confounding by additional recorded or unrecorded variables cannot be completely excluded in our cohort study—even though a similar proportion of subjects in each cohort were found to have comorbid conditions that were analyzed in the study (microvascular and macrovascular complications of diabetes, similar mean estimated glomerular filtration rate). Finally, similar to real-life clinical practices, patient- and provider-level factors likely determined the management preferences for a particular insulin regimen in this study.

Our focus on well-controlled patients, managed by well-resourced endocrinologists in a public health care system, may limit the generalizability of the study findings to diabetes populations with suboptimal glycemic control in association with larger GV and those managed in other health systems. However, the VARIATION study criteria were specifically chosen to minimize the impact of mean glucose control (and A1C) on GV parameters among the four cohorts. It should be emphasized that despite the low SD values observed, our study found a significant difference among cohorts in all three measures of SD as well as in hypoglycemia outcomes.

In conclusion, the lowest glucose variability as well as hypoglycemia on continuous glucose monitoring were observed for the GLP-1 RA + basal insulin combination among the four equal VARIATION study insulin cohorts having good mean glucose control. Further research is needed to confirm these findings in varied populations and to investigate further the potential long-term effects, including the possibility of CV benefits, related to the GV and hypoglycemia benefits of using a combination of basal long-acting insulin and GLP-1 RAs.

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