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Effect of Dapagliflozin as an Add-on Therapy to Insulin on the Glycemic Variability in Subjects with Type 2 Diabetes Mellitus (DIVE): A Multicenter, Placebo-Controlled, Double-Blind, Randomized Study

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Background: Glycemic variability is associated with the development of diabetic complications and hypoglycemia. However, the effect of sodium-glucose transporter 2 (SGLT2) inhibitors on glycemic variability is controversial. We aimed to examine the effect of dapagliflozin as an add-on therapy to insulin on the glycemic variability assessed using continuous glucose monitoring (CGM) in subjects with type 2 diabetes mellitus.
Methods: In this multicenter, placebo-controlled, double-blind, randomized study, 84 subjects received 10 mg of dapagliflozin (n=41) or the placebo (n=43) for 12 weeks. CGM was performed before and after treatment to compare the changes in glycemic variability measures (standard deviation [SD], mean amplitude of glycemic excursions [MAGEs]).
Results: At week 12, significant reductions in glycosylated hemoglobin (–0.74%±0.66% vs. 0.01%±0.65%, P<0.001), glycated albumin (–3.94%±2.55% vs. –0.67%±2.48%, P<0.001), and CGM-derived mean glucose (–41.6±39.2 mg/dL vs. 1.1±46.2 mg/dL, P<0.001) levels were observed in the dapagliflozin group compared with the placebo group. SD and MAGE were significantly decreased in the dapagliflozin group, but not in the placebo group. However, the difference in ΔSD and ΔMAGE failed to reach statistical significance between two groups. No significant differences in the incidence of safety endpoints were observed between the two groups.
Conclusion: Dapagliflozin effectively decreased glucose levels, but not glucose variability, after 12 weeks of treatment in participants with type 2 diabetes mellitus receiving insulin treatment. The role of SGLT2 inhibitors in glycemic variability warrants further investigations.

Keywords: Dapagliflozin; Diabetes mellitus; Randomized controlled trial; Sodium-glucose transporter 2 inhibitors

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INTRODUCTION

Glucose variability, which refers to oscillations or fluctuations in blood glucose levels, is associated with various adverse health outcomes [1,2]. Although certain degree of variability in biological parameters is a physiological phenomenon, glucose variability is often excessively increased in patients with diabetes and has been identified as an independent driver of diabetic complications and mortality [3-8]. Therefore, strategies that reduce glucose variability are becoming an emerging treatment target for patients with diabetes, in addition to controlling fasting hyperglycemia, postprandial hyperglycemia and increased glycosylated hemoglobin (HbA1c) levels. Based on this information, researchers are focusing on whether a specific class of glucose-lowering agents also stabilize glucose fluctuations.

Sodium-glucose transporter 2 (SGLT2) inhibitors, including dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and ipragliflozin, have been approved as a new class of glucose-lowering compounds for the treatment of type 2 diabetes mellitus [9]. Inhibition of SGLT2 in renal proximal tubules improves glucose homeostasis by reducing the maximum renal glucose reabsorptive capacity and threshold at which glucose is excreted in the urine [10]. The effect of SGLT2 inhibitors depends on the degree of hyperglycemia and renal function, and is characterized by an insulin-independent mode of action [11]. The risk of hypoglycemia is low due to the compensatory role of SGLT1 in the downstream late proximal tubule and counterregulatory mechanisms, including an increase in plasma glucagon levels and hepatic gluconeogenesis [12-14]. Therefore, SGLT2 inhibitors would conceivably be effective in reducing glucose variability.

Several published studies have examined the effects of SGLT2 inhibitors on glucose variability, in both patients with type 1 and type 2 diabetes mellitus [15-25]. However, most of the studies were performed with a relatively small number of subjects and short-term treatment, producing conflicting results. In this study, we aimed to examine the effect of dapagliflozin as an add-on to insulin on the glycemic variability assessed using continuous glucose monitoring (CGM) in subjects with type 2 diabetes mellitus and inadequate glycemic control.

METHODS

Compliance with ethical standards

The study protocol was approved by Institutional Review Board of each participating center (Seoul St. Mary's Hospital: XC14MIMV0103K), and all subjects provided written informed consent before participation. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Study design and subjects

This multicenter, placebo-controlled, double-blind, randomized clinical trial (ClinicalTrials.gov identifier: NCT02459353) was conducted at six centers in South Korea between August 2015 and December 2016. Eligible participants were patients with type 2 diabetes mellitus who were receiving greater than 0.2 IU/kg/day of basal insulin±metformin or sulfonylurea for at least 12 weeks. Patients aged 20 to 70 years with an HbA1c level of 7.0% to 10.0% at screening were recruited. Participants were randomized to receive 10 mg of dapagliflozin or placebo for 12 weeks. Randomization was stratified based on an HbA1c level of 8.0% and the study site. The maintenance of the same dose of insulin and oral hypoglycemic agents during the study period was recommended, although insulin could be titrated in the event of hypoglycemia or hyperglycemia and based on the physician's discretion. The key exclusion criteria included people with type 1 diabetes mellitus (fasting C-peptide ≤0.6 ng/dL), secondary diabetes or gestational diabetes; use of insulin other than basal insulin; a history of diabetic ketoacidosis or hyperglycemic hyperosmolar state; an estimated glomerular filtration rate <60 mL/min/1.73 m^2; abnormal liver function as defined by aspartate aminotransferase (AST)/alanine aminotransferase (ALT) >3 times the upper normal limit; a history of chronic cystitis or recurrent urinary tract infection; use of loop diuretics or medications known to affect glucose metabolism; a history of malignancy within 5 years; a history of acute coronary syndrome, stroke or coronary artery bypass graft within 6 months; New York Heart Association class III or IV congestive heart failure; and participation in a weight loss program or use of anti-obesity medications.

Continuous glucose monitoring

CGM was performed two times, before randomization and after the completion of 12 weeks treatment, using the Minimed CGM System Gold or iPro2 (Medtronic, Northridge, CA, USA). Glucose data were obtained for 72 hours, and the mean amplitude of glycemic excursions (MAGE) and standard deviation (SD) of glucose were calculated. The sensor was inserted on day 1 and removed on day 4 at both visits. We also calculat-

ed MAGE and SD over 48 hours, from 00:00 hours on the second day of CGM sensor insertion to 24:00 hours on the third day. MAGE was defined as the mean of the absolute difference from nadir to peak or from peak to nadir for those differences that exceeded the SD [26]. For the efficacy variables derived from CGM, analyses using 48 hour data are mainly presented. Analyses using 72 hour data produced similar results (data not shown).

Efficacy and safety assessments

The primary endpoint was to evaluate the effect of dapagliflozin on glucose variability compared to the placebo after 12 weeks of treatment. The extent of changes in MAGE and SD were compared between the two groups. Secondary endpoints included a comparison of glycemic control variables (fasting plasma glucose, HbA1c, glycated albumin, and mean glucose levels, as well as the time-in-target range [70 to 180 mg/dL] obtained from CGM), blood pressure, lipid profiles, body weight and changes in body mass index (BMI) between two groups. Safety and tolerability were also assessed from overall adverse events, serious adverse events and adverse events of special interest, which included hypoglycemia, severe hypoglycemia, genital infection, urinary tract infection, dehydration and hypovolemia. Severe hypoglycemia was defined as hypoglycemic events requiring assistance. Anthropometric and laboratory data were collected at baseline and 6 and 12 weeks after treatment.

Statistical analyses

The sample size was calculated by assuming that the mean MAGE difference between the dapagliflozin group and placebo group would be at least 20 mg/dL (SD=30 mg/dL). Approximately 37 subjects in each group were needed to detect a significant difference with a power of 0.8 and statistical significance of 0.05 (α). Considering a 20% drop-out rate, the target enrollment number was 90 subjects. The intention-to-treat (ITT) population included all randomized patients who received at least one dose of the study drug. The per-protocol (PP) population was defined as a subset of the ITT population who completed the study without any major protocol violations. The efficacy analyses were performed both on ITT and PP populations. The last observation carried forward imputation technique was used to handle missing values. The PP population was analyzed for the presentation of efficacy variables derived from CGM. The safety analyses were performed on the ITT population. Data are presented as mean±SD or numbers (%). The independent *t*-test or Wilcoxon rank sum test were used to compare of continuous variables, and the chi-square or Fisher's exact test were used to compare categorical variables, as appropriate. A paired *t*-test or Wilcoxon signed rank test was also applied to compare pre- and post-treatment values. A *P* value <0.05 was considered statistically significant, and all analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, USA).

RESULTS

Participant disposition and characteristics

One hundred seventeen subjects were screened and 84 were randomized (41 to the dapagliflozin group and 43 to the placebo group). Of the randomized subjects, 66 completed the study (Supplementary Fig. 1). Baseline demographics and efficacy parameters were generally balanced between the treatment groups (Table 1). The mean age and BMI were 57.7 years and 26.6 kg/m^2 in the placebo group, and 59.7 years and 27.3 kg/m^2 in the dapagliflozin group, respectively. The mean duration of diabetes was 15.1 years in both groups. No significant differences in fasting glucose (137.4±53.5 mg/dL vs. 145.6±56.4 mg/dL), HbA1c (8.25%±0.69% vs. 8.30%±0.77%) and fasting C-peptide (1.78±1.27 ng/dL vs. 1.60±1.19 ng/dL) levels were observed between the placebo and dapagliflozin groups. Only systolic BP and background medication differed between two groups.

Efficacy

The 24 hours urine glucose excretion was significantly increased in the dapagliflozin group (Supplementary Fig. 2). After 12 weeks of treatment, the mean changes in the HbA1c (–0.74%±0.66% vs. 0.01%±0.65%, *P*<0.001) and glycated albumin (–3.94%±2.55% vs. –0.67%±2.48%, *P*<0.001) levels from the baseline values were significantly greater in the group treated with dapagliflozin compared with the placebo (Fig. 1). Fasting glucose levels were significantly decreased by the dapagliflozin treatment, but not the placebo (Table 2). The 48 hours mean glucose levels derived from CGM were also significantly decreased in the dapagliflozin group, but not in the placebo group (–41.6±39.2 mg/dL vs. 1.1±46.2 mg/dL, *P*<0.001) (Fig. 2A). Glucose variability indices, SD and MAGE, were significantly decreased by dapagliflozin after 12 weeks of treatment compared with baseline values. However, ΔSD (–7.64±18.75

Table 1. Baseline characteristics of the study participants

Characteristic	Placebo (n=43)	Dapagliflozin (n=41)	P value
Age, yr	57.7±7.3	59.7±8.0	0.087
Male sex	18 (41.9)	17 (41.5)	0.971
Height, cm	159.9±9.8	161.3±8.5	0.478
Body weight, kg	68.3±11.0	71.3±13.9	0.540
Body mass index, kg/m^2	26.6±3.0	27.3±3.9	0.421
Systolic BP, mm Hg	120.3±12.0	126.5±11.4	0.017
Diastolic BP, mm Hg	76.6±8.2	77.4±7.5	0.274
Heart rate, bpm	75.2±8.0	79.2±10.9	0.056
DM duration, yr	15.1±6.0	15.1±7.2	0.990
Fasting glucose, mg/dL	137.4±53.5	145.6±56.4	0.420
HbA1c, %	8.25±0.69	8.30±0.77	0.840
Fasting C-peptide, ng/dL	1.78±1.27	1.60±1.19	0.463
Hemoglobin, g/dL	14.2±1.5	13.8±1.3	0.227
Serum creatinine, mg/dL	0.80±0.16	0.78±0.18	0.725
eGFR, mL/min/1.73 m^2	85.6±12.3	87.1±17.4	0.661
Smoking			0.856
Current	5 (11.6)	6 (14.6)	
Ex-smoker	9 (20.9)	7 (17.1)	
Non-smoker	29 (67.4)	28 (68.3)	
Hypertension	29 (67.4)	25 (61.0)	0.536
Dyslipidemia	36 (83.7)	32 (78.1)	0.508
Medical treatment			0.006
Insulin only	1 (2.3)	0	
Insulin+MET	12 (27.9)	7 (17.1)	
Insulin+SU	7 (16.3)	4 (9.8)	
Insulin+MET+SU	23 (53.5)	30 (73.2)	

Values are presented as mean±standard deviation or number (%).
BP, blood pressure; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; eGFR, estimated glomerular filtration rate; MET, metformin; SU, sulfonylurea.

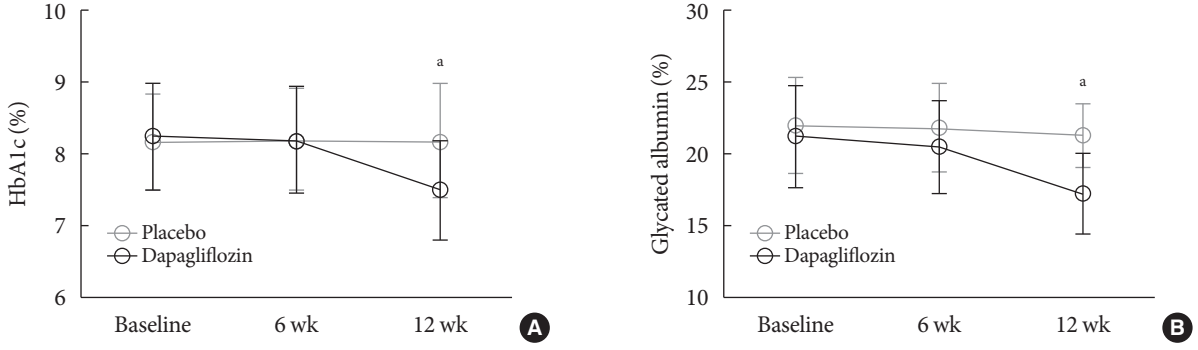

Fig. 1. (A) Glycosylated hemoglobin (HbA1c) and (B) glycated albumin levels recorded during the study. Values are presented as mean±standard deviation. [a]P<0.05 for the comparison between groups.

Table 2. Changes in metabolic and laboratory markers in the two groups

Variable	Placebo (n=43)			Dapagliflozin (n=41)		
	Baseline	6 wk	12 wk	Baseline	6 wk	12 wk
Body weight, kg	68.3±11.0	68.1±11.2	67.9±11.6	71.3±13.8	70.8±14.0[a]	70.1±14.0[a]
Body mass index, kg/m^2	26.6±3.0	26.6±3.1	26.5±3.3	27.3±3.9	27.1±3.9[a]	26.8±4.0[a]
Fasting glucose, mg/dL	137.4±53.5	136.2±48.7	136.3±41.6	145.6±56.4	142.7±55.8	124.0±29.3[a,b]
Insulin dose, U/day	29.9±10.7	29.3±10.8[a]	29.4±11.2	35.0±16.7	32.3±16.9[a]	31.5±16.9[a]
Systolic BP, mm Hg	121.8±11.9	123.7±11.6	122.4±11.8	125.2±10.9	125.0±9.3	123.0±9.6
Diastolic BP, mm Hg	76.3±8.4	76.7±7.6	77.5±7.9	77.7±7.7	78.0±7.4	77.4±7.9
Hemoglobin, g/dL	14.2±1.4	14.2±1.4	14.2±1.5	13.7±1.3	13.8±1.3	14.5±1.6[a,b]
BUN, mg/dL	15.1±4.0	15.2±3.6	16.1±4.0	15.0±4.5	15.6±4.6	16.7±4.4[a]
Creatinine, mg/dL	0.80±0.17	0.80±0.17	0.79±0.16	0.77±0.16	0.78±0.16	0.80±0.18[a]
Uric acid, mg/dL	4.52±1.28	4.49±1.17	4.62±1.29	4.59±1.30	4.56±1.30	4.46±1.31[a,b]
eGFR, mL/min/1.73 m^2	85.3±12.8	85.3±12.9	86.1±12.7	87.7±16.2	87.5±16.6	85.4±19.6[a,b]
AST, IU/L	25.3±8.7	25.2±8.7	27.1±14.7	26.6±13.7	26.5±13.7	23.6±9.8[a]
ALT, IU/L	27.6±11.4	27.2±11.3	29.3±14.4	28.4±16.8	29.6±19.1	23.1±9.5[a,b]
Total cholesterol, mg/dL	158.8±34.4	159.4±32.3	159.2±36.9	157.1±33.5	154.6±30.9	160.6±32.9
Triglycerides, mg/dL	137.4±65.6	147.1±84.1	146.4±110.9	140.9±77.3	136.3±72.4	144.7±80.9
HDL-C, mg/dL	46.3±8.8	46.4±8.9	46.7±8.4	44.1±7.9	44.1±8.0	45.0±8.8
LDL-C, mg/dL	86.8±28.6	86.1±26.0	85.2±29.0	85.3±25.0	83.7±24.5	88.1±28.1

Values are presented as mean±standard deviation.
BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.
[a]P<0.05 compared with baseline values, [b]P<0.05 compared with the placebo group.

mg/dL vs. −4.09±22.62 mg/dL, P=0.494) and ΔMAGE (−23.09±55.18 mg/dL vs. −11.34±57.61 mg/dL, P=0.341) were not significantly different between the dapagliflozin and placebo groups (Fig. 2B and C). Analyses of groups stratified by baseline HbA1c levels (8%), BMI (25 kg/m^2), duration of diabetes (10 years), insulin dose (0.6 IU/kg), median value of homeostasis model assessment of insulin resistance or beta-cell function, and the presence or absence of hypoglycemia identified using CGM revealed similar results in all subgroups (data not shown). Analyses using the ITT dataset also produced similar results (data not shown). In the dapagliflozin group, subjects with improved glucose variability were characterized by a lower BMI than subjects with increased variability (26.5±3.4 kg/m^2 vs. 29.4±4.1 kg/m^2, P=0.044).

Compared with baseline values, the mean percentage of time in which CGM glucose values were within the target range (70 to 180 mg/dL) increased, whereas time within the hyperglycemic range (>180 mg/dL) decreased following the dapagliflozin treatment. No significant changes were noted in the placebo group. At 12 weeks after the treatment, the dapagliflozin group showed higher percentage of time within the target range and with hypoglycemic range, but a lower percentage of time within the hyperglycemic range, than placebo group (Fig. 3).

In the dapagliflozin group, body weight, BMI, insulin dose, and uric acid, AST, and ALT levels were significantly decreased at 12 weeks compared with the baseline values. Furthermore, uric acid and ALT levels were significantly reduced by the dapagliflozin treatment compared with the placebo. A subtle but significant decrease in eGFR levels was observed in the dapagliflozin group. No significant changes were detected in the blood pressure and lipid profiles between the two groups or before and after treatment (Table 2).

Safety

Measures of adverse events were generally similar between groups. The percentage of subjects experiencing one or more adverse events was 17.1% in the dapagliflozin group and 11.6% in the placebo group (P=0.476) (Supplementary Table 1). No

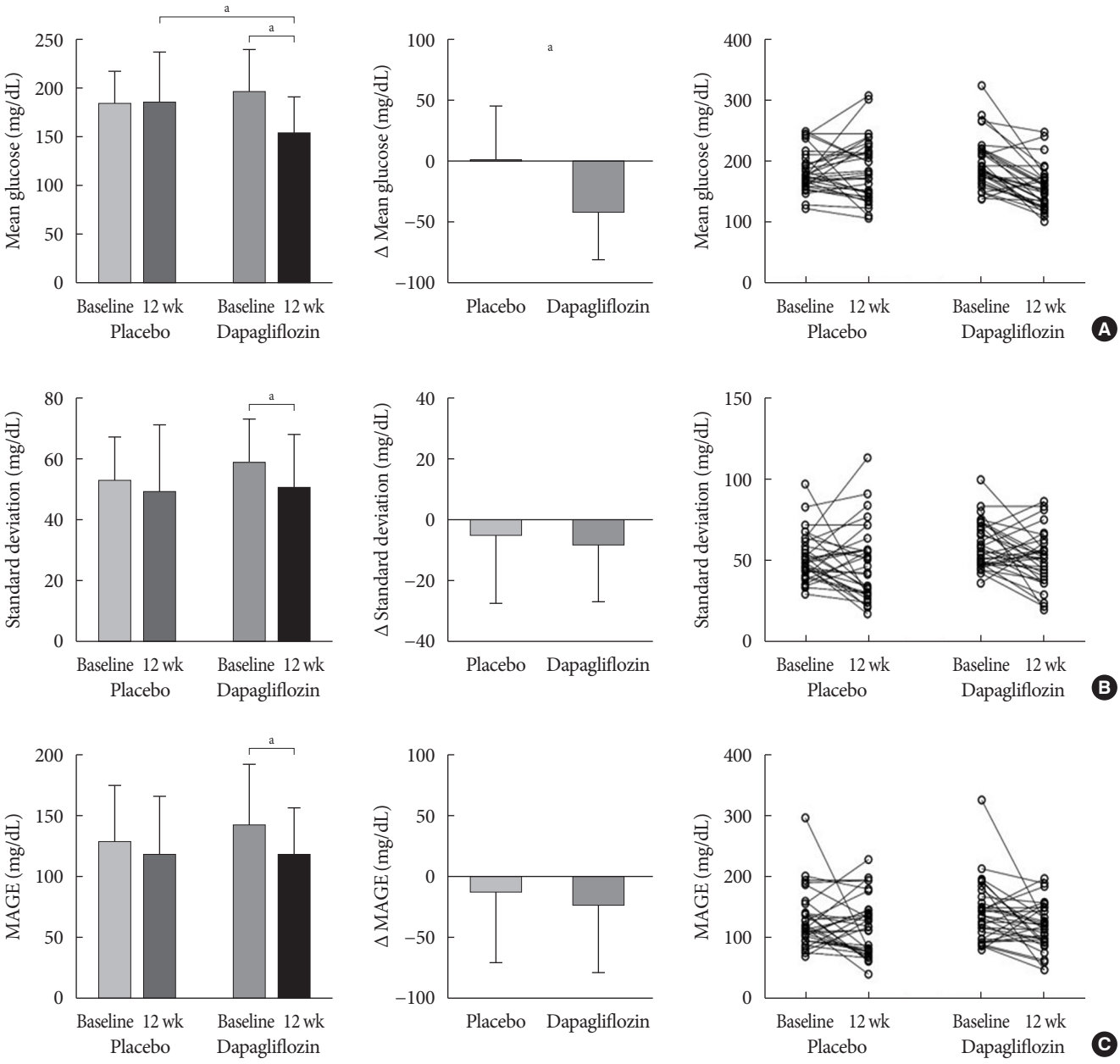

Fig. 2. (A) Mean glucose levels, (B) standard deviation, and (C) mean amplitude of glycemic excursion (MAGE) derived from continuous glucose monitoring. The right panel shows individual plots from participants. Values are presented as mean±standard deviation. [a]$P<0.05$.

significant difference in the occurrence of hypoglycemia was noted between two groups, and no severe hypoglycemic episodes occurred during the study (Supplementary Table 2).

DISCUSSION

In this randomized, placebo-controlled trial, we tested whether 12 weeks of treatment with dapagliflozin improved glucose variability in patients with type 2 diabetes mellitus and inadequate glycemic control who were receiving insulin. The dapagliflozin treatment significantly decreased the fasting glucose, HbA1c, glycated albumin, and mean glucose levels obtained from CGM, and increased the time-in-target range. However, changes in the degree of glucose variability were insignificant

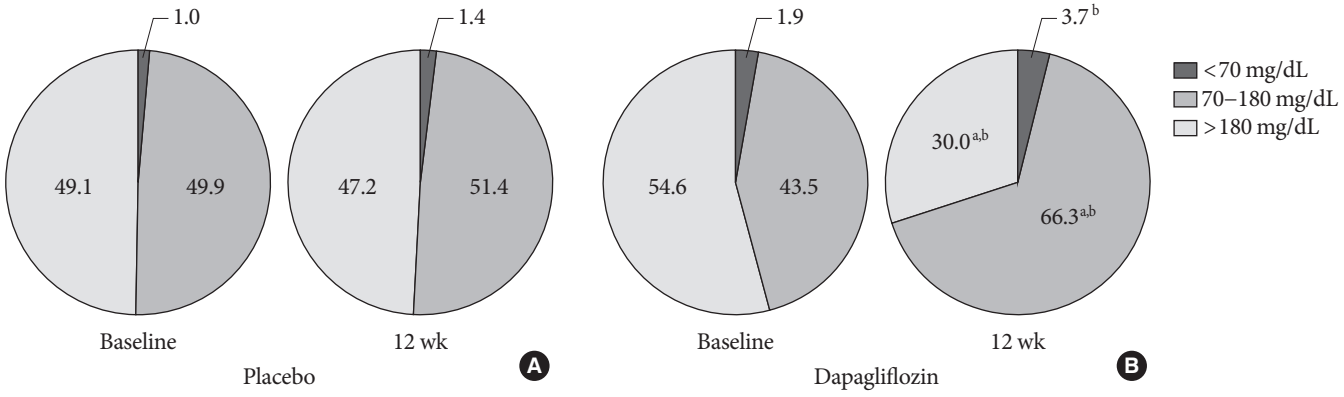

Fig. 3. Percentage of time in which glucose levels were within the target range, hyperglycemia, and hypoglycemia in the (A) placebo and (B) dapagliflozin groups. [a]$P<0.05$ compared with baseline, [b]$P<0.05$ compared with the placebo group.

compared with the placebo group.

Glucose variability and HbA1c variability, which reflect short-term and long-term glycemic fluctuation, respectively, have been linked to various complications and mortality in both subjects with type 1 and type 2 diabetes mellitus [4-8]. An analysis of glucose and HbA1c data obtained from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial revealed that visit-to-visit glucose variability was associated with both micro- and macrovascular events and HbA1c variability was associated with both vascular events and mortality [4]. A cohort study in China showed an independent association between fasting plasma glucose variability and all-cause mortality in patients with type 2 diabetes mellitus and poor glycemic control [7]. A meta-analysis of seven studies of patients with type 1 diabetes mellitus and thirteen studies of patients with type 2 diabetes mellitus also confirmed that HbA1c variability represents a possible independent risk factor for micro- and macrovascular complications and mortality. Although most previous studies employed a retrospective design, and intentional control of glucose variability is difficult to achieve in a prospective study, the consistency observed from multiple studies strengthens the relationship between glucose variability and adverse health outcomes. Mechanistically, apoptosis was increased in human umbilical vein endothelial cells exposed to alternating 5 or 20 mmol/L glucose which was more deleterious than constant exposure to high glucose [27]. This difference was associated with elevated levels of nitrotyrosine and 8-hydroxydeoxyguanosine, suggesting that glucose fluctuations induce oxidative stress [28]. In humans, 24-hour urinary excretion rates of free 8-iso prostaglandin $F_{2\alpha}$, another estimate of oxidative stress, were significantly correlated with MAGE after adjustment for multiple factors [29]. Collectively, data from clinical trials and in vitro studies clearly emphasize the importance of targeting glucose variability for achieving better outcomes in patients with diabetes.

From this perspective, the effects of different classes of antidiabetic agents on glucose variability have been studied in various clinical trials. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, which act in a glucose-dependent manner, or α-glucosidase inhibitors and prandial insulins, which lowers postprandial glucose levels have shown to be more effective in stabilizing glucose fluctuations than other agents, such as sulfonylurea or basal insulin [3,30-33]. A clear conclusion regarding the effect of SGLT2 inhibitors on glucose variability appears to be premature. In patients with type 1 diabetes mellitus, short-term treatment with empagliflozin or sotagliflozin as an add-on to insulin improves glucose variability [18,20]. Eighteen to 24 weeks of treatment with canagliflozin or sotagliflozin also improve the time-in-range measured using CGM [23,25]. However, an exploratory study in which patients were treated with dapagliflozin for 2 weeks failed to show a significant difference in changes in SD or MAGE compared with the placebo, although a dose-dependent reduction in glucose variability was observed [15]. In patients with type 2 diabetes mellitus, short-term treatment with empagliflozin or luseogliflozin as a monotherapy improves mean glucose levels or time-in-range, but a significant difference in glucose variability indices is not observed compared with the placebo [16,17]. A single-arm study in which canagliflozin was added to insulin therapy revealed reductions in SD, MAGE, and the mean of the daily difference in blood glu-

cose levels (MODD), whereas switching from a DPP-4 inhibitor to dapagliflozin had no effect on reducing glucose variability in patients with type 2 diabetes mellitus receiving insulin [21,22]. A recent study evaluating the effect of a 4 weeks dapagliflozin treatment showed improvements in glucose variability when dapagliflozin was added to metformin monotherapy, but not when added to insulin therapy [24]. Our results are consistent with some of the previous studies [15,24] showing that the extent to which dapagliflozin decreases glucose variability is insignificant compared with the placebo, although changes compared with the baseline values are observed in patients when this treatment is added to insulin treatment.

Various explanations may account for the inconsistent results, including differences in characteristics of study subjects, background medications, treatment duration, type of comparator, and the selectivity of SGLT2 inhibitors. In particular, when SGLT2 inhibitors are used in combination with insulin or sulfonylurea, the risk of hypoglycemia is potentially increased. In a study examining the kinetics of renal glucose transport using hyperglycemic clamp, empagliflozin treatment reduced maximal renal glucose transport and the plasma glucose concentration threshold for glucose spillage in the urine to <40 mg/dL in both healthy individuals and patients with type 2 diabetes mellitus [34]. Based on this finding, SGLT2 inhibitors might induce renal glucose excretion at levels less than the normal plasma glucose concentration. Another study using the hyperglycemic clamp in patients with type 2 diabetes mellitus reported a proportional increase in renal glucose excretion with increasing blood glucose levels. Glucosuria persisted when the blood glucose concentration decreased to the euglycemic level, suggesting that the classical concept of a renal threshold for glucose excretion is not supported in subjects with diabetes [35]. Notably, we and other groups showed a slight increase in the hypoglycemic range in the CGM analysis over time in patients treated with SGLT2 inhibitors, which might exert a negative effect on glucose variability [24]. Researchers have proposed that the actions of SGLT2 inhibitors are mitigated by compensatory glucose reabsorption by SGLT1, glucagon secretion from pancreatic alpha cells and increased endogenous glucose production, which might exert positive effects on reducing the hypoglycemia risk. Further investigations are needed to determine whether these findings are class effects.

The strength of this study is that we recruited a large number of subjects compared to previous studies examining the effects of SGLT2 inhibitors on glucose variability in patients with type 2 diabetes mellitus receiving insulin. However, one important limitation is that we were unable to introduce a standardized diet during CGM because this study was performed in an ambulatory care setting, which might have exaggerated the glucose variability.

In conclusion, the addition of dapagliflozin therapy to insulin in subjects with type 2 diabetes mellitus and inadequate glycemic control was effective in lowering glucose levels and generally tolerable, consistent with previous trials. Although reductions in glucose variability parameters were observed within the dapagliflozin group, the values were not significantly different from the placebo group. Larger clinical trials employing a diet-controlled CGM analysis would be helpful to better characterize the relationship between SGLT2 inhibitors and glucose variability.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2019.0203.

CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

Conception or design: S.H.L., K.H.Y.
Acquisition, analysis, or interpretation of data: S.H.L., K.W.M., B.W.L., I.K.J., S.J.Y., H.S.K., Y.H.C., K.H.Y.
Drafting the work or revising: S.H.L.
Final approval of the manuscript: S.H.L., K.W.M., B.W.L., I.K.J., S.J.Y., H.S.K., Y.H.C., K.H.Y.

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