Comparison of Gemigliptin and Dapagliflozin Effects on Glycemic Variability in Type 2 Diabetes: A Randomized, Open-Label, Active-Controlled, 12-Week Study (STABLE II Study)

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Comparison of the effects of gemigliptin and dapagliflozin on glycaemic variability in type 2 diabetes: A randomized, open-label, active-controlled, 12-week study (STABLE II study)

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Abstract

Aims: The aim of this study was to compare the effect of gemigliptin, a dipeptidyl peptidase-4 inhibitor, and dapagliflozin, a sodium glucose co-transporter-2 inhibitor, on glycaemic variability in type 2 diabetes patients.

Materials and methods: In this randomized, blinded end point, multicentre clinical trial, we enrolled 71 patients with type 2 diabetes who were inadequately controlled with metformin alone or were drug naïve. The participants were randomized to receive gemigliptin 50 mg (n = 35) or dapagliflozin 10 mg (n = 36) daily for 12 weeks. Glycaemic variability was estimated by mean amplitude of glycaemic excursions (MAGE), standard deviation (SD) and coefficient of variation (CV) using a 6-day continuous glucose monitoring system. The primary efficacy endpoint was change in MAGE after 12 weeks compared to baseline.

Results: Intergroup differences in baseline characteristics were not significant. The adjusted mean change (± standard error) in MAGE after 12 weeks in the gemigliptin

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and dapagliflozin groups was −27.2 ± 4.4 mg/dL and −7.9 ± 4.9 mg/dL, respectively. Between-group comparisons showed a significantly larger reduction in MAGE in the gemigliptin group (−19.2 mg/dL; 95% CI, −31.3 to −7.2; P = .002). Measures of SD and CV also showed a significantly larger reduction in the gemigliptin group. Average glycaemic control, estimated by HbA1c, fasting glucose and safety profiles, was comparable between the two groups.

Conclusions: Compared to dapagliflozin, gemigliptin significantly improved glycaemic variability, with similar glucose-lowering efficacy and safety profiles in patients with type 2 diabetes who were inadequately controlled with metformin alone or were drug naïve.

1 | INTRODUCTION

Optimal glucose control is determined, not only by the average glucose level, but also by glycaemic variability.[1] Thus far, the average glucose level estimated using HbA1c has been the primary marker of long-term glucose control and is an established predictor of diabetic vascular complications. Recently, it has been suggested that glycaemic variability may reflect the excess risk of diabetic complications that are not explained by the average glucose or HbA1c level, as well as the risk of hypoglycaemia.[2,3] There are several glucose metrics that reflect glycaemic variability; these include the coefficient of variation (CV), standard deviation (SD) and mean amplitude of glycaemic excursion (MAGE). Among them, MAGE mainly reflects meal-related glycaemic excursion and has been suggested to be associated with vascular complications[4] and mortality[5] in type 2 diabetes patients. In previous studies, oxidative stress and inflammatory markers were associated with increased glucose variability.[3]

Both dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium glucose co-transporter 2 (SGLT2) inhibitors are widely used as add-on therapy for patients with type 2 diabetes who are inadequately controlled with metformin,[6] or as first-line therapy for those who are unable to tolerate metformin.[7] However, it is not clear which of the two would be preferential in the absence of increased cardiovascular risk or a previous event of cardiovascular disease. One of the major strengths of these two classes of antidiabetic medications is that they are associated with a minimal risk of hypoglycaemia when used as monotherapy.[8,9] In addition, they do not result in weight gain, and SGLT2 inhibitors can even induce weight loss.[9] DPP-4 inhibitors have been shown to decrease glycaemic variability as they stimulate glucose-dependent insulin secretion and inhibit glucagon production.[10] SGLT2 inhibitors increase urinary glucose excretion and their actions are also dependent on plasma glucose concentration, at least in part.[11] However, they do not have a preferential effect on postprandial glucose excursion and might increase the glucagon level. Recently, there have been reports suggesting that SGLT2 inhibitors may have beneficial effects on glycaemic variability.[12] Still, the evidence is scarce and requires further investigation.

We hypothesized that there could be a difference between the two widely used classes of antidiabetic medication in terms of their effect on glycaemic variability. To test this hypothesis, we specifically investigated whether gemigliptin, a DPP-4 inhibitor, is superior in reducing MAGE compared to dapagliflozin, an SGLT2 inhibitor, in patients with type 2 diabetes who are inadequately controlled with metformin alone or in drug-naïve patients. In addition, we examined the association between glycaemic variability and oxidative stress and inflammatory markers as an indicator of vascular complications.

2 | RESEARCH DESIGN AND METHODS

2.1 | Study design

This 12-week, phase 4, multicentre, parallel group, prospective, randomized, open-blinded end-point (PROBE) study was conducted at eight sites in the Republic of Korea between July 2017 and July 2018. The study included a 4-week screening period and a 12-week active treatment period. Eligible patients underwent continuous glucose monitoring (CGM) (iPro2, Medtronic MiniMed, Northridge, California) for 6 days at baseline and were randomized to receive either gemigliptin or dapagliflozin in a 1:1 ratio, with stratification by baseline HbA1c (<8.5% or ≥8.5%) and with metformin being the background antidiabetic drug. Randomization was performed using the Interactive Web Response System (cubeIWRS®, CRScube, Inc., Republic of Korea). Participants received the assigned study drug (gemigliptin 50 mg or dapagliflozin 10 mg) every morning, maintained exercise levels and diet control, and visited the study site at Week 4 and Week 12. After 12 weeks of treatment, the participants underwent CGM for 6 days while continuing the study drug. During the CGM period, it was recommended that participants maintain their regular diet and exercise regime, and this was evaluated using a diary card. Drug compliance was evaluated by the pharmacist by comparing the dispensed and the returned quantity of study drug at each visit. The study (ClinicalTrials.gov: NCT03202563) was conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and standard operating procedures of the sponsor. The study was approved by the institutional review board of each site and written informed consent was obtained before the screening procedure.

2.2 | Study population

Eligible participants were men and women aged 20 to 70 years, with a diagnosis of type 2 diabetes, an HbA1c level between 7% and 11%,

and who had not received antidiabetic agents for at least 8 weeks before screening or who were inadequately controlled with metformin alone (HbA1c >7% with use of metformin for >12 weeks with a stable dose of ≥1000 mg/day for ≥4 weeks before screening). Exclusion criteria and rescue therapy criteria are described online in Supporting Information (Appendix S1). Briefly, patients with a body mass index (BMI) >40 kg/m^2 and an estimated glomerular filtration rate (eGFR)[13] <60 mL/min/1.73 m^2 were excluded. Participants undergoing stable dose metformin monotherapy at screening continued this treatment throughout the study period.

2.3 | Glucose profile using CGM

CGM was performed for 144 hours (6 days) from the morning of Day 1 to Day 7. The time period for MAGE evaluation was pre-defined as the stabilized signal period, which is a total of 72 hours (3 days) from 12:00 AM on Day 2 after CGM sensor insertion (Day 1) to 12:00 AM on Day 5. Although most previous studies measured glycaemic variability for a period of 24 or 48 hours,[12,14,15] we decided to perform CGM for a total of 72 hours to evaluate glycaemic variability with better accuracy. Participants who were unable to provide 72-hour data were excluded from the glycaemic variability analysis. Among the randomized participants, MAGE could not be evaluated in several because of inability to collect CGM data for unknown reasons (gemigliptin group [n = 1], dapagliflozin group [n= 5]), lack of a stabilized signal period (gemigliptin group [n = 1], dapagliflozin group [n = 2]), drop-out (gemigliptin group [n = 1], dapagliflozin group [n = 2]), and visit-window deviation (dapagliflozin group [n = 3]). For assessing MAGE, the peak and nadir glucose values with an absolute difference exceeding 1 SD (over 3 days) were ascertained. The difference between peak and subsequent nadir blood glucose levels or between the nadir and subsequent peak glucose levels was recorded, and their mean was calculated.[16] To reinforce the reliability of the study results, MAGE values were manually calculated, independently, by a blinded central evaluator.

2.4 | Efficacy and safety assessment

Change in MAGE at Week 12 compared to baseline was the primary efficacy endpoint. Secondary efficacy endpoints included: change from baseline at Week 12 in MBG, SD and CV; percentage of time with hypoglycaemia (<70 mg/dL), normoglycaemia (≥70-≤180 mg/dL), hyperglycaemia level I (>180 mg/dL) and hyperglycaemia level II (>250 mg/dL) and area under the curve $(AUC)_{0\text{-}72h}$ or area over the curve $(AOC)_{0\text{-}72h}$ during the CGM period; high-sensitivity C-reactive protein (hsCRP); nitrotyrosine and HbA1c; fasting plasma glucose (FPG); fasting serum insulin; glycated albumin; homeostasis model assessment of β-cell function (HOMA-β) and homeostasis model assessment of insulin resistance (HOMA-IR)[17]; total cholesterol; triglycerides (TG); LDL cholesterol; HDL cholesterol; BMI; and body weight.

Safety assessment included vital signs, clinical laboratory measurements and adverse events, defined as all adverse and unintended symptoms, signs or diseases regardless of study drug causality throughout the study. Data concerning hypoglycaemic events, defined as a plasma glucose level <70 mg/dL or any event requiring assistance attributable to hypoglycaemia, were collected. Details of laboratory measurements and safety monitoring are described online in Supporting Information (Appendix S1).

2.5 | Statistical analysis

A total of 70 participants (35 per group, including 20% drop-out rate) were considered to achieve 80% power with a one-sided significance level of 2.5%, assuming a treatment difference of −21.3 mg/dL and SD of 29.2 mg/dL and 20.5 mg/dL for gemigliptin and dapagliflozin, respectively.[10,18] The primary endpoint was investigated using an analysis of covariance (ANCOVA) model, with baseline MAGE as a covariate and HbA1c (<8.5% or ≥8.5%) and use of a background antidiabetic agent (metformin) as factors. For other efficacy endpoints, the baseline value of each dependent variable was used as a covariate. Two-sided 95% confidence interval (CI) for adjusted mean difference (gemigliptin vs dapagliflozin) was calculated. If the upper bound of the CI was less than 0, gemigliptin was considered superior to dapagliflozin.

Descriptive statistics were used for secondary endpoints and the difference between groups was also determined using ANCOVA. For efficacy endpoints including HbA1c and FPG, missing values were replaced by the last observation carried forward method if data were obtained after baseline. The difference in baseline characteristics between groups was determined by two-sample t-test or Wilcoxon's rank sum test for continuous data and by chi-square test or Fisher's exact test for categorical data. Efficacy evaluation was performed primarily with the full analysis set (FAS), which comprised randomized participants who received the study drug at least once and for whom MAGE or any central laboratory results after randomization were available. Data are presented as adjusted mean ± standard error, with the exception of baseline data, which are presented as mean ± SD. Safety analysis included all randomized participants who received the study drug at least once. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, North Carolina).

3 | RESULTS

3.1 | Demographics and baseline characteristics

During the study period, 91 participants were screened and 71 were randomized. Among them, one and three subjects dropped out from the gemigliptin and dapagliflozin groups, respectively, resulting in 67 participants completing the 12-week study. A total of 70 participants (gemigliptin group [n = 34], dapagliflozin group [n = 36]) were included in the FAS (Figure S1 in the Appendix S1). MAGE was analysed in 32 and 23 participants in the gemigliptin and dapagliflozin groups, respectively.

The mean age of participants was 53.6 ± 9.2 years and 50.5 ± 11.2 years in the gemigliptin and dapagliflozin groups, respectively,

and the corresponding percentage of male participants was 58.8% and 72.2%, respectively (Table 1). The mean HbA1c level at baseline was 7.9% in both the gemigliptin and dapagliflozin groups. There was a nonsignificant small difference in proportion of participants who received metformin as background therapy because of an error in study group assignment for three participants (gemigliptin group, 50.0%; dapagliflozin group, 63.9%; P = .241). In the FAS, mean drug compliance was 97.4% and 97.6% in the gemigliptin and dapagliflozin groups, respectively. There was no noteworthy deviation from ordinary diet or exercise regime during the CGM period.

3.2 | Glucose-lowering efficacy and MAGE

After 12 weeks, HbA1c, FPG and glycated albumin significantly decreased in both groups (P < .001) (Table 2). The adjusted mean change in HbA1c from baseline was −1.3% ± 0.1% in the gemigliptin group and −1.0 ± 0.1% in the dapagliflozin group. The between-group difference was −0.24% (95% CI, −0.51 to 0.03; P = .079) and was not statistically significant.

The MAGE at baseline and at Week 12 was 89.2 ± 28.8 mg/dL and 60.6 ± 20.3 mg/dL in the gemigliptin group, respectively (Figure 1). The corresponding values in the dapagliflozin group were 89.0 ± 31.1 mg/dL and 79.7 ± 32.5 mg/dL, respectively. The adjusted mean change from baseline to Week 12 in MAGE was −27.2 ± 4.4 mg/dL (P < .001) and −7.9 ± 4.9 mg/dL (P = .160) in the gemigliptin and dapagliflozin groups, respectively. The reduction in MAGE from baseline was significant only in the gemigliptin group. The between-group difference was −19.2 mg/dL (95% CI, −31.3 to −7.2; P = .002) and the gemigliptin group showed a greater reduction than that obtained in the dapagliflozin group. The interaction between the covariate (baseline MAGE) and treatment group was statistically significant (P = .011). However, the result of ANCOVA with the interaction term was similar to that of ANCOVA without the interaction term, and gemigliptin was still superior to dapagliflozin in reducing MAGE (Table S1 in the Appendix S1).

TABLE 1 Demographics and baseline characteristics

Full analysis set	Gemigliptin (N = 34)	Dapagliflozin (N = 36)	*P* value
Demographic and clinical characteristics			
Age, year	53.6 ± 9.2	50.5 ± 11.2	.214[a]
Male, n (%)	20 (58.8%)	26 (72.2%)	.238[b]
Duration of diabetes, year	2.2 ± 2.2	3.5 ±3 .8	.324[c]
BMI, kg/m^2	26.0 ± 3.6	25.6 ± 3.7	.916[c]
HbA1c, %	7.9 ± 0.9	7.9 ± 0.7	.557[c]
eGFR, mL/min/1.73m^2	98.3 ± 17.8	108.4 ± 22.9	.076[c]
Background therapy, n (%)			
Use of metformin	17 (50.0%)	23 (63.9%)	.241[b]
Drug compliance during the study period, %			
Drug compliance	97.4%	97.6%	.777[c]

Note: Data are expressed as mean ± standard deviation, unless otherwise indicated.

Abbreviation: BMI, body mass index; FPG, fasting plasma glucose.

[a]Two sample t-test.

[b]Pearson's chi-square test.

[c]Wilcoxon's rank sum test.

3.3 | Secondary outcomes of glycaemic variability

Intergroup differences in the secondary endpoints SD and CV at baseline were not significant. Adjusted mean change in SD and CV from baseline to Week 12 was −11.8 ± 1.9 mg/dL (P < .001) and −0.04 ± 0.01 (P = .005), respectively, in the gemigliptin group (Figure 1). The corresponding values in the dapagliflozin group were −3.9 ± 2.1 mg/dL (P = .204) and 0.01 ± 0.01 (P = .353), respectively. The between-group difference in SD and CV was −8.0 mg/dL (95% CI, −13.1 to −2.8; P = .003) and −0.05 (95% CI, −0.07 to −0.02; P = .001), respectively. The gemigliptin group showed a significantly greater reduction in SD and CV compared to that of the dapagliflozin group. There was no between-group difference in MBG reduction from baseline to Week 12 (95% CI, −15.3 to 6.6; P = .427).

Subgroup analyses according to HbA1c level (<8.5% or ≥8.5%) and metformin as background therapy were performed for glycaemic variability parameters (Table S2). A significant reduction in MAGE was observed in the two subgroups of the gemigliptin group. It appeared that a greater reduction in MAGE with gemigliptin was shown in the metformin subgroup. Additional analysis of glycaemic variability was performed during the day and during the night. The change in SD, CV and MBG during the day and during the night was similar to that of the daily results (Table S3).

The mean glucose profile over 72 hours for both groups is presented online in Figure S2. Both groups showed significant changes in the percentage of time with hyperglycaemia level I (>180 mg/dL) and hyperglycemia level II (>250 mg/dL) and in $AUC_{0\text{-}72h}$ for both levels from baseline at Week 12 (Figure 2). The gemigliptin group showed a significantly decreased percentage of time with hyperglycaemia level II (>250 mg/dL) and in $AUC_{0\text{-}72h}$ for both hyperglycaemia levels compared to the corresponding results obtained for the dapagliflozin group. The percentage of time with a normoglycaemia level (≥70-≤180 mg/dL) significantly increased in both groups. More weight loss and improvement in HOMA-IR were observed in the dapagliflozin group compared to the gemigliptin group (Table 2). However, there was no correlation between weight loss and reduction in HOMA-IR or improvement in MAGE in the dapagliflozin group (Table S4).

3.4 | Exploratory analysis and safety results

Intergroup differences in the change in inflammatory and oxidative stress markers such as hsCRP and nitrotyrosine after 12 weeks were not significant. However, only the gemigliptin group showed a significant decrease in hsCRP from baseline at Week 12 (Table 2). During the study, six (17.1%) and seven (19.4%) participants reported adverse events in the gemigliptin and dapagliflozin groups, respectively, regardless of study drug causality. No adverse drug reaction occurred in the gemigliptin group, whereas one participant (2.8%) experienced two adverse drug reactions in the dapagliflozin group (alanine aminotransferase increase and

TABLE 2 Change in efficacy parameters at Week 12

Parameters		Gemigliptin (N = 34)	Dapagliflozin (N = 36)	*P* value
Metabolic parameters				
HbA1c (%)	Baseline	7.9 ± 0.9	7.9 ± 0.8	
Change at Week 12		−1.3 ± 0.1[b]	−1.0 ± 0.1[b]	.079
HbA1c (mmol/mol)	Baseline	62.9 ± 9.9	63.0 ± 9.0	
Change at Week 12		−13.8 ± 1.4[b]	−11.2 ± 1.3[b]	.079
FPG (mg/dL)	Baseline	149.6 ± 32.2	158.4 ± 36.5	
Change at Week 12		−32.3 ± 3.7[b]	−32.2 ± 3.6[b]	.980
Glycated albumin (%)	Baseline	20.3 ± 5.21	20.6 ± 3.96	
Change at Week 12		−4.98 ± 0.49[b]	−4.41 ± 0.46[b]	.327
Fasting serum insulin (uIU/mL)	Baseline	11.5 ± 6.2	11.6 ± 9.3	
Change at Week 12		2.3 ± 1.0	−1.0 ± 0.9	.011
HOMA- β	Baseline	56.4 ± 37.5	50.2 ± 43.1	
Change at Week 12		38.9 ± 9.4[b]	31.5 ± 8.9[a]	.530
HOMA-IR (mg/dL)	Baseline	4.1 ± 2.1	4.5 ± 3.5	
Change at Week 12		−0.2 ± 0.3	−1.5 ± 0.3[a]	.004
Total cholesterol (mg/dL)	Baseline	165.2±36.6	150.1±36.8	
Change at Week 12		−9.5 ± 4.7[a]	−4.6 ± 4.4	.403
LDL cholesterol (mg/dL)	Baseline	95.0 ± 31.3	85.2 ±33.4	
Change at Week 12		−4.1 ± 4.7	−4.9 ± 4.5	.884
HDL cholesterol (mg/dL)	Baseline	51.0 ± 15.3	48.5 ± 10.8	
Change at Week 12		0.6 ± 1.6	4.1 ± 1.5[a]	.085
Triglyceride (mg/dL)	Baseline	166.0 ± 97.1	135.4 ± 70.0	
Change at Week 12		−15.1 ± 10.9	−6.38 ± 10.4	.530
Body weight (kg)	Baseline	70.8 ± 13.3	71.0 ± 12.4	
Change at Week 12		0.3 ± 0.5	−2.2 ± 0.4[b]	<.001
Inflammatory and oxidative stress parameters				
hsCRP (mg/L)	Baseline	1.4 ± 2.6	1.4 ± 1.3	
Change at Week 12		−0.5 ± 0.3[a]	0.1 ± 0.3	.121
Nitrotyrosin (nM)	Baseline	93.1 ± 30.0	105 ± 51.4	
Change at Week 12		15.0 ± 10.5	21.7 ± 10.0	.612

Note: Data are from FAS and are presented as adjusted mean ± standard error except baseline data, which are presented as mean ± SD; data were analysed using an ANCOVA model with the baseline value of each variable as a covariate and HbA1c (<8.5% or ≥8.5%) and existence of background anti-diabetic agent (metformin) as factors.

[a]$P < .05$ vs baseline, paired t-test or Wilcoxon's signed rank test.

[b]$P < .001$ vs baseline, paired t-test or Wilcoxon's signed rank test.

aspartate aminotransferase increase) (Tables S5 and S6). There was no reported serious adverse event in the gemigliptin group. One participant in the dapagliflozin group reported a serious adverse event, which involved hospitalization that was not related to the study drug. Hypoglycaemia was not reported in either group and no urinary tract infection or genital infection was reported.

4 | DISCUSSION

In this randomized, multicentre, 12-week clinical trial (PROBE) involving 71 participants with type 2 diabetes, who were either using metformin or drug naïve, we showed that gemigliptin and dapagliflozin were both effective in lowering the average glucose level, as estimated by HbA1c. Compared to the dapagliflozin group, the gemigliptin group showed a significantly larger reduction in MAGE at Week 12, which was the primary outcome. This finding was supported by the results obtained for secondary outcomes, which also revealed significantly larger reductions in SD and CV in the gemigliptin group than those in the dapagliflozin group. Both medications were well tolerated. Urinary tract infections and genital infections were not observed in the dapagliflozin group, probably because of the small number of female participants.

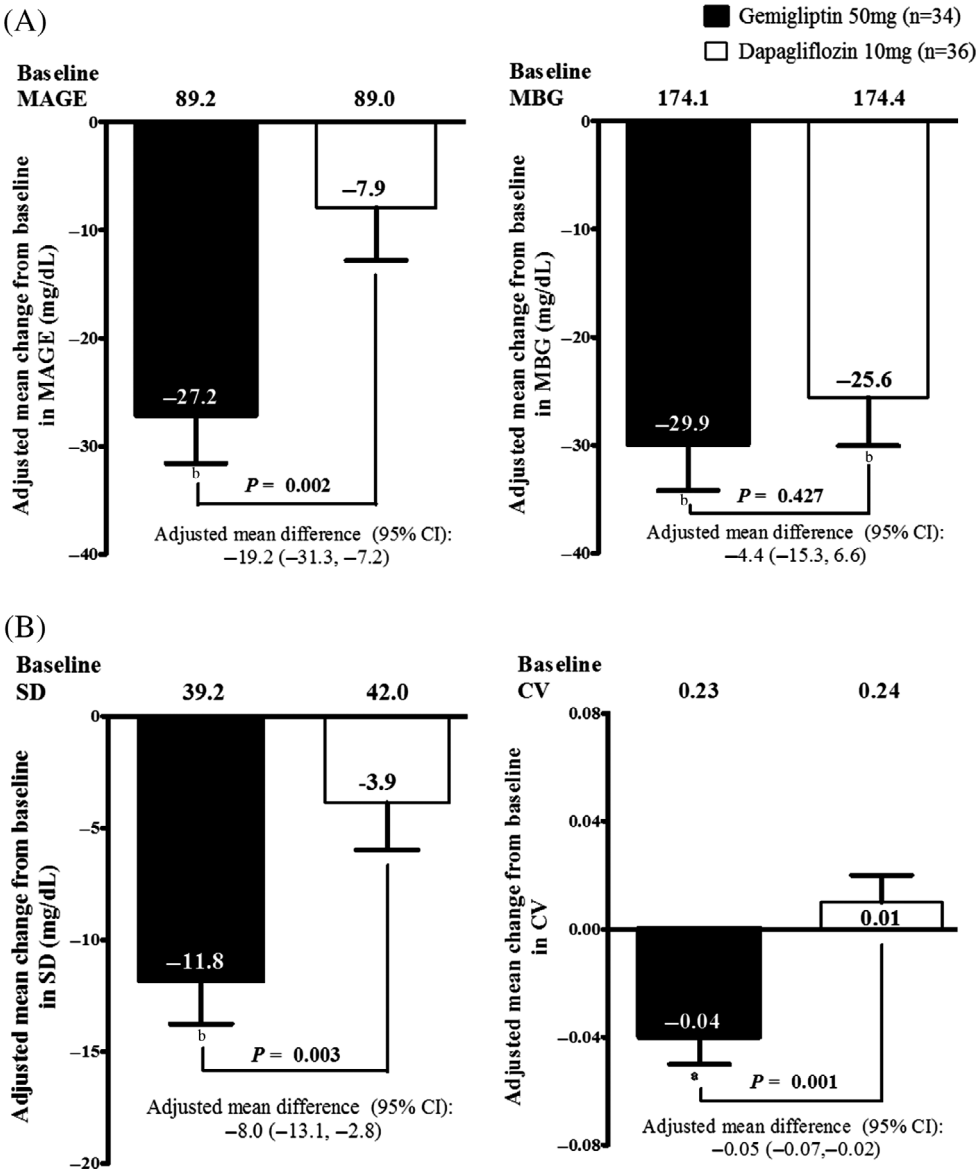

FIGURE 1 Adjusted mean change from baseline to Week 12 in MAGE (A), MBG (B), SD (C) and CV (D) with gemigliptin and dapagliflozin. Values are given as means ± standard error. ANCOVA analysis adjusted for baseline value of each variable, HbA1c (<8.5% or ≥8.5%) and existence of use of metformin. Abbreviations: CV, coefficient of variation; MAGE, mean amplitude of glycaemic excursion; MBG, mean blood glucose; SD, standard deviation. **P* < .01 vs baseline; ***P* < .001 vs baseline

It has been well known that DPP-4 inhibitors reduce glycaemic variability.[10,19-21] MAGE was significantly decreased after treatment with vildagliptin, compared to baseline, in Italian patients with type 2 diabetes, as well as in Korean patients.[20-22] Treatment with gemigliptin and sitagliptin also resulted in a similar decrease in MAGE in patients with poorly controlled type 2 diabetes in Korea.[10] However, reports of the effects of SGLT2 inhibitors on glycaemic variability have been conflicting. One-week treatment with luseogliflozin did not reduce MAGE in Japanese patients with type 2 diabetes.[15,23] In contrast, 4-week treatment with dapagliflozin decreased MAGE (−15.3 mg/dL) in patients with type 2 diabetes in the USA.[24] Various factors, including treatment duration and the study drug, might account for these discrepancies. In this head-to-head comparison study, gemigliptin was superior, compared to dapagliflozin, in reducing MAGE. This is the first study to directly compare the effects of gemigliptin, a DPP-4 inhibitor, and dapagliflozin, an SGLT2 inhibitor, on glycaemic variability using CGM in drug-naïve patients with type 2 diabetes or those undergoing metformin monotherapy.

The average glucose level, reflected by HbA1c and MBG, was reduced to a similar degree in both groups. The difference in MAGE between the two groups is thought to be attributable to the reduced meal-related glycaemic excursion in the gemigliptin group. The significant reduction in time spent with a glucose level above 250 mg/dL and $AUC_{0\text{-}72h}$ with a glucose level above 180 mg/dL or above 250 mg/dL in the gemigliptin group compared to that in the dapagliflozin group supports this notion. This is relevant also because MAGE was developed originally to reflect meal-related glycaemic excursion, as it is more sensitive to deviation toward hyperglycaemia.[1,25,26] There was a larger reduction of SD in the gemigliptin group, which is in accord with the greater reduction in MAGE and reflects the fact that MAGE is well correlated with SD.[27]

The mechanism underlying gemigliptin's superior ability to improve glycaemic variability at a degree relatively similar to that of

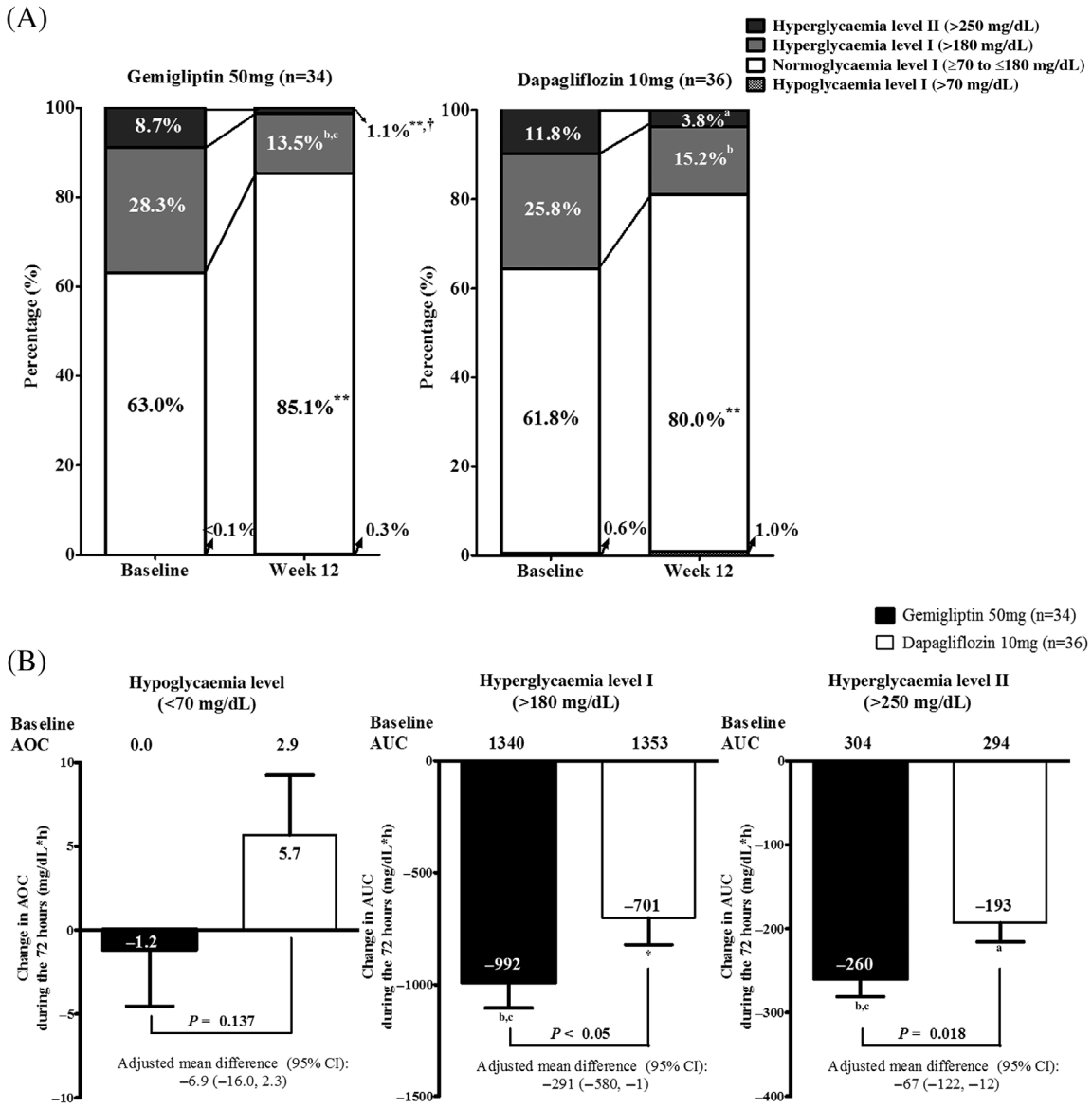

FIGURE 2 A, Percentage of time with hypoglycaemia, normoglycaemia, hyperglycaemia level I and II and B, adjusted mean change in $AUC_{0\text{-}72h}$/$AOC_{0\text{-}72h}$. Baseline is mean and Week 12 is adjusted mean in both groups. Abbreviation: AUC, Area under the curve; AOC, Area over the curve. The linear trapezoidal method was used to calculate AUC or AOC. During the glycaemic variability evaluation period (0~72 hours), the $AUC_{0\sim72h}$ and $AOC_{0\sim72h}$ were calculated as the area corresponding to more than 180 or 250 mg/dL and as the area corresponding to less than 70 mg/dL, respectively. *P < .05 vs baseline. **P < .001 vs baseline. ***P < .05 vs dapagliflozin group

HbA1c improvement, compared to that of dapagliflozin, is unclear. The larger reduction in glycaemic variability in the gemigliptin group seems to be independent of weight loss and improved HOMA-IR, as these factors were more prominent in the dapagliflozin group. It could be speculated that the glucagon level might explain the difference in glycaemic variability between the two groups, at least in part. One of the key pathophysiologies of type 2 diabetes is α-cell dysfunction and hyperglucagonaemia, which results in both fasting and postprandial hyperglycaemia.[28] It has been reported that, compared to SGLT2 inhibition by dapagliflozin, DPP-4 inhibition by vildagliptin results in a 5% lower fasting and postprandial glucagon level after 2 weeks of treatment in type 2 diabetes patients.[29] In addition, compared to SGLT2 inhibition, DPP-4 inhibition resulted in more rapid insulin secretion, with higher C-peptide, intact GLP-1 and glucose-dependent insulinotropic polypeptide levels.[29] These might have resulted in reduced variability between fasting and postprandial glucose in the gemigliptin group. In contrast, dapagliflozin elicited parallel downward shifts in both fasting and postprandial glucose levels. This is our potential explanation for the difference in glycaemic variability between the two groups, despite the similar decrease in HbA1c.

It has been hypothesized that glycaemic variability is associated with diabetic complications.[30,31] In a previous report, glycaemic variability was associated with increased systemic oxidative stress, which is thought to be a key factor in the pathophysiology of diabetic

complications.[3] In a previous report, reduction in MAGE was associated with decreased levels of nitrotyrosine, interleukin-6 and interleukin-8.[21] However, in our study, we did not observe a significant difference in the change in the inflammatory marker, hs-CRP, and the oxidative stress marker, nitrotyrosine, between the two groups. In addition, there was no association between changes in MAGE and hsCRP or nitrotyrosine (data not shown). This could be explained by several factors, including small sample size, the short duration of diabetes in our study population, and difference in baseline HbA1c. Further investigations are required to understand the way in which reducing glycaemic variability can be translated into clinical outcomes.

This study has certain limitations. First, MAGE data for approximately 22.5% (n = 16) of the study participants could not be analysed. This is explained, for the most part, by an inability to reach a stabilized signal period of 72 hours in CGM analysis (n = 3), drop-out before 12 weeks (n = 4) and detection failure of sensor signals because of unknown causes (n = 6). The missing rate was slightly higher in this study than that in previous studies.[12,14,15] It should be noted that, in our study, a 72-hour period was used to investigate MAGE compared to other studies that used only 24 hours[12,14,15] or 48 hours.[3,21] In a sensitivity analysis using a 48-hour period, the difference in MAGE between the two groups did not change (Table S7). Second, this was an open-label study; still, MAGE was independently estimated by a blinded central evaluator and the allocation data were concealed. Third, there was an insignificant difference in background therapy between the two groups because of human errors. Fourth, as the study drug was continued during the post-intervention CGM period, it was difficult to determine whether the reduced glycaemic variability was a result of acute or long-term exposure to the study drug. Finally, this was a relatively short-term study and we had limitations in translating our MAGE findings into meaningful clinical outcomes. Further large-scale, long-term studies are required.

In conclusion, this study is the first to directly compare the effect of DPP-4 inhibition and SGLT2 inhibition on glycaemic variability estimated by MAGE. Gemigliptin significantly improved MAGE, SD and CV compared to dapagliflozin after 12 weeks of treatment, although there was a similar degree of reduction in HbA1c in patients with type 2 diabetes who were drug naïve or undergoing metformin monotherapy.

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CONFLICT OF INTEREST

S. L. is an employee of LG Chem, Ltd. None of the other authors has potential conflicts of interest relevant to this study.

AUTHOR CONTRIBUTIONS

All authors participated in the design of the study. All authors except S. L conducted the study and contributed to data acquisition. S. H. K drafted and revised the manuscript for important intellectual content and interpreted the data. Y. C. H., S. Y. K. and J. H. K interpreted the data and reviewed the manuscript for important intellectual content. All authors reviewed and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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