Glucose excursions and hypoglycemia in patients with type 2 diabetes treated with mitiglinide/voglibose versus glimepiride: A randomized cross-over trial*

Kanta FUJIMOTO,1,2* Yui SHIBAYAMA,1 Eriko YAMAGUCHI,1 Sachiko HONJO,1 Akihiro HAMASAKI1 and Yoshiyuki HAMAMOTO1,3

1Center for Diabetes and Endocrinology, Tazuke Kofukai Foundation Medical Research Institute Kitano Hospital, Osaka, Japan, 2Department of Diabetes and Endocrinology, Kobe City Medical Center General Hospital, Kobe, Japan, and 3Center for Diabetes and Endocrinology, Kansai Electric Power Hospital, Osaka, Japan

Abstract

Background: Glucose excursions and hypoglycemia are associated with cardiovascular complications. However, no studies have evaluated glucose excursions and the frequency of hypoglycemia in patients treated with mitiglinide/voglibose versus glimepiride as add-on to the dipeptidyl peptidase-4 (DPP-4) inhibitor.

Methods: This cross-over trial included 20 patients with type 2 diabetes. After initiating vildagliptin 100 mg, patients were randomly assigned to receive mitiglinide 10 mg/voglibose 0.2 mg three times daily for 3 days followed by glimepiride 1 mg once daily for the subsequent 3 days as add-on therapy, or vice versa. Glucose excursions and hypoglycemia frequency were measured using 24-h continuous glucose monitoring. Metabolic profile changes were evaluated using a meal tolerance test.

Results: The mean glucose levels in the mitiglinide/voglibose and glimepiride phases were identical (8.01 vs 8.24 mmol/L, respectively). However, during the mitiglinide/voglibose phase compared with the glimepiride phase, the standard deviation of glucose (1.30 vs 2.10 mmol/L; P < 0.001), mean amplitude of glycemic excursions (3.47 vs 5.28 mmol/L; P < 0.001), M-value (24.6 vs 70.0; P < 0.001), continuous overlapping net glycemic action for a 1-h time interval (22.6 vs 31.0; P < 0.001), and area under the curve >10 mmol/L (0.18 vs 0.52 mmol/L per h; P < 0.001) were significantly lower. Hypoglycemia (glucose <3.8 mmol/L) was not observed during the mitiglinide/voglibose phase, but occurred 0.35 times/day in those taking glimepiride. Moreover, the mitiglinide/voglibose phase had higher premeal and lower post-meal glucose levels than the glimepiride phase.

Conclusions: Adding mitiglinide/voglibose to vildagliptin therapy results in more efficient postprandial glucose control and less hypoglycemia than adding glimepiride.

Highlights

• This is the first randomized cross-over trial using continuous glucose monitoring to compare glucose excursions and hypoglycemia frequency in patients with type 2 diabetes treated with mitiglinide/voglibose versus glimepiride as add-on to the dipeptidyl peptidase-4 (DPP-4) inhibitor.
• The mean glucose levels in the mitiglinide/voglibose and glimepiride phases were identical, but fewer glucose excursions and no episodes of hypoglycemia were observed with mitiglinide/voglibose.
• Mitiglinide/voglibose as an add-on to a DPP-4 inhibitor may be a suitable therapeutic option for preventing cardiovascular events.
Introduction

Long-term hyperglycemia, reflected by high HbA1c levels, affects diabetes complications.\(^1\) In addition to high HbA1c levels, postprandial glucose excursions and hypoglycemia are thought to be related to cardiovascular complications. An association between cardiovascular disease and postprandial or postload hyperglycemia has been reported in clinical studies such as the Diabetes Epidemiology Collaborate Analysis of Diabetic Criteria in Europe (DECODE) study\(^2\) and the Funagata study.\(^3\) In addition, many large cohort studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD)\(^4\) and the Action in Diabetes and Vascular Disease (ADVANCE)\(^5\) studies have shown that hypoglycemia also increases the risk of cardiovascular events and mortality. Therefore, glycemic control using medication should aim to reduce glycemic excursions by lowering postprandial glucose levels while avoiding hypoglycemia. Many current guidelines and reports place great significance on HbA1c levels, but HbA1c does not reflect exact glycemic excursions. Several methods or markers, based on continuous glucose monitoring (CGM), which can evaluate glycemic excursions, have been established and are used clinically.\(^6\) Moreover, detection of hypoglycemia in clinical trials is often suboptimal because it is commonly assessed by means of measured blood glucose levels or symptoms; this is a particular problem if hypoglycemic events are asymptomatic. Thus, CGM may be a useful and accurate tool to evaluate glycemic trends and hypoglycemia in clinical trials.

Dipeptidyl peptidase-4 (DPP-4) inhibitors are broadly used in clinical practice. They stimulate insulin secretion in a glucose-dependent manner; hence, DPP-4 inhibitor monotherapy rarely causes hypoglycemia. However, when inadequate glucose control is obtained with DPP-4 inhibitor monotherapy, additional medications, such as insulin or other oral antidiabetic drugs, are required. Although the addition of sulfonylureas to DPP-4 inhibitor therapy is cost effective and simple, this may increase the risk of hypoglycemia. Among the oral antidiabetic drugs, glinides, α-glucosidase inhibitors (αGIs), and DPP-4 inhibitors are known to reduce postprandial glucose levels. Considering the actions of these drugs, the combination of a glinide and an αGI may be a reasonable therapy for patients with postprandial hyperglycemia. However, because glinides have insulinotropic actions similar to sulfonylureas, there is some concern about the possibility of hypoglycemia.

In Japan, a fixed-dose combination tablet comprising mitiglinide 10 mg and voglibose 0.2 mg was approved for use in 2011. No studies have compared the effects of mitiglinide/voglibose versus glimepiride on glucose variability and hypoglycemia using CGM. Furthermore, many studies investigating glucose variability and oral antidiabetic agents were conducted primarily in Caucasians, so that the results are not necessarily applicable to Asian populations. Therefore, in the present study, we evaluated glucose excursions and the frequency of hypoglycemic episodes in patients using mitiglinide/voglibose compared with those using glimepiride when these drugs were used as an add-on to DPP-4 inhibitor therapy.

Methods

The aim of the present study was to investigate the differences in glucose excursions and episodes of hypoglycemia in patients with type 2 diabetes mellitus (T2DM) treated with mitiglinide/voglibose or glimepiride in a cross-over manner.

Patients

Adult Asian patients with T2DM who were admitted to Kitano Hospital to establish glycemic control were enrolled in the present study. Patients with insulin-dependent diabetes (defined as a fasting serum C-peptide level < 0.5 ng/mL), renal failure (creatinine clearance < 40 mL/min), hepatic dysfunction (serum aspartate aminotransferase or alanine aminotransferase levels more than two times the upper limit of normal), known allergies to mitiglinide, voglibose, or glimepiride, diabetic retinopathy at a higher stage than moderate non-proliferative, and those taking corticosteroids were excluded from the study.

Study design

The present study was an open-label single-center randomized cross-over trial conducted between April 2013 and October 2014. Except for metformin, pioglitazone, or vildagliptin, all other antidiabetic medicines used before the trial were discontinued. All patients were established on treatment with the DPP-4 inhibitor.
vildagliptin (100 mg) for more than 2 days. Once vildagliptin treatment was initiated, patients were randomly assigned to either the addition of mitiglinide 10 mg/voglibose 0.2 mg three times daily for 3 days followed by glimepiride 1 mg once daily for the subsequent 3 days or the addition of glimepiride 1 mg once daily for 3 days followed by mitiglinide 10 mg/voglibose 0.2 mg three times daily for 3 days. Simple randomization was performed using sequentially numbered papers. Random allocation was concealed from everyone, including the patients and physicians, until the interventions were assigned. Subjects were issued with a CGM system (iPro2; Medtronic MiniMed, Northridge, CA, USA) to monitor glycemic excursions throughout the study period (the evaluation period was the last day of both phases). The adjustment from sensor values to plasma glucose levels was performed based on calibration by means of self-monitoring of blood glucose at least four times daily. During the initial period of DPP-4 inhibitor use only, subjects were allowed to use pre-meal insulin aspart and/or morning insulin glargine U-100 if premeal plasma glucose levels were high (>10 mmol/L), provided that the last insulin administration was >2.5 days for insulin aspart and > 3 days for insulin glargine before the evaluation periods were scheduled. Mitiglinide 10 mg/voglibose 0.2 mg was administered as a fixed-dose combination drug (Kissei Pharma, Matsumoto, Japan) three times daily before meals. Glimepiride 1 mg (Sanofi, Gentilly, France) was administered after breakfast. Standard meal tolerance tests (MTT) containing approximately 500 kcal (60% carbohydrate, 20% protein, and 20% fat) were conducted after an overnight fast on the last day of both treatment phases, and changes in metabolic profiles were evaluated. The study strategy is shown in Fig. 1.

The study protocol was approved by the Ethics Committee of Kitano Hospital, where the study was conducted, and the study was performed in accordance with the principles of the Declaration of Helsinki. All study participants provided written informed consent at the time of enrollment. This study is registered with University Hospital Medical Information Network Clinical Trials Registry (ID: UMIN000024817).

### Efficacy parameters

The primary efficacy endpoint was the difference in glycemic excursions between the two phases, assessed by analyzing 24-h CGM data on the last day of each treatment phase. To minimize possible carryover effects, there was a 2-day period before each CGM period instead of having a washout period. This interval also provided almost enough time (>4 days) for stabilization of vildagliptin treatment. The following efficacy measures were assessed: glycemic variability, including the standard deviation (SD) of sensor glucose levels measured via CGM, the mean amplitude of glycemic excursions (MAGE), the M-value, the continuous overlapping net glycemic action for a 1-h time interval (CONGA 1), and the area under the curve (AUC) >10 mmol/L. The MAGE was obtained by measuring the arithmetic mean of the changes >1 SD between sequential peaks and nadirs; this method has been widely used to assess glycemic fluctuation and variability.\(^7\) The M-value was calculated for each glucose value using a formula and was then divided by the total number of values to produce a mean.\(^8\) The CONGA 1 value represents the SD of differences between the current period and the period 1 h earlier.\(^9\) The mean glucose level was obtained by averaging the 288 sensor values measured during the 24-h CGM period.

The secondary endpoint was the difference in the frequency of hypoglycemic episodes (glucose level < 3.8 mmol/L) during the 24-h CGM period. During the MTT, metabolic profile changes in plasma glucose, insulin, and glucagon levels from premeal to 120 min after the meal were measured by standard radioimmunoassays.

### Diet and exercise

The diet during the study period was determined to provide a total caloric intake of 25–30 kcal/kg per day, with approximately 60% of calories derived from carbohydrates, 20% from proteins, and 20% from fats. Meals were served at 0800 hours (breakfast), 1200 hours (lunch), and 1800 hours (dinner). During the study period, patients were asked to exercise as previously and not to change the exercise intensity and period according to their capability.
**Table 1** Baseline characteristics of the study subjects (n = 20)

| Characteristic                        | Value          |
|---------------------------------------|----------------|
| Age (years)                           | 65.6 ± 11.5    |
| Male                                  | 10 (50)        |
| BMI (kg/m²)                           | 25.6 ± 3.8     |
| Duration of diabetes (years)          | 10.7 ± 8.7     |
| HbA1c (%)                             | 9.4 ± 3.4      |
| HbA1c (mmol/mol)                      | 79 ± 16        |
| FPG (mmol/L)                          | 7.53 ± 1.44    |
| HOMA-β                                | 2.5 ± 1.0      |
| HOMA-β                                | 39.9 ± 17.7    |
| eGFR (mL/min/1.73 m²)                 | 75.3 ± 21.5    |

Complications
- Retinopathy: 8 (40)
- Nephropathy: 6 (30)
- Neuropathy: 13 (65)
- Macroangiopathy: 5 (25)

Medications used before the trial
- Sulfonylurea: 11 (55)
- Metformin: 6 (30)
- Pioglitazone: 1 (5)
- DPP-4 inhibitor: 11 (55)
- αGI: 4 (20)

Data are given as the mean ± SD or as n (%).

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; FPG, fasting plasma glucose; HOMA-β, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; eGFR, estimated glomerular filtration rate; αGI, α-glucosidase inhibitor.

### Statistical analysis

Because comparative data on the primary endpoints of both therapies have not been published, sample size calculations were based on the feasibility of conducting a study and clinical considerations, referencing results of a similar study that used CGM. An assumed the detectable difference between therapies of 0.52 mmol/L and an SD of 0.53 mmol/L for the “SD of glucose” as the primary endpoint were established. Using a two-sided significance level of 0.05 and power of 80% in a cross-over study with an estimated dropout rate of 5%, we estimated that a sample size of 20 participants was required.

Considering the possible carryover effect of both therapies due to non-washout (“sequence effect”), we performed subanalyses stratified by the order of drug use. In addition, efficacy endpoints were analyzed using an intention-to-treat approach with a linear mixed-effect model with treatment, sequence, and period as fixed effects and patients as a random effect. Normally distributed data are presented as the mean ± SD and effect sizes between therapies are presented as the standardized effect size of least square mean with bias-corrected (Hedges’ g). Statistical analyses were performed using JMP 13 (SAS Institute, Cary, NC, USA) and statistical significance was defined as \( P < 0.05 \).

### Results

Twenty patients were enrolled in the study, and there was no attrition. The baseline characteristics of the study subjects are given in Table 1. More than 50% of patients had been treated with DPP-4 inhibitors before participating in this trial.

Glucose fluctuations, assessed by 24-h CGM, are shown in Fig. 2. The mean glucose levels of the mitiglinide/voglibose and glimepiride phases were very similar (8.01 ± 1.33 and 8.24 ± 1.61 mmol/L, respectively; \( P = 0.184 \); Table 2). However, postprandial glucose levels were lower in the mitiglinide/voglibose than glimepiride phase, with a lower SD of glucose (1.30 ± 0.45 vs 2.10 ± 0.61 mmol/L, respectively; \( P < 0.001 \)), MAGE (3.47 ± 1.28 vs 5.28 ± 2.15 mmol/L, respectively; \( P < 0.001 \)), M-value (24.6 ± 27.2 vs 70.0 ± 61.9, respectively; \( P < 0.001 \)), CONGA 1 value (22.6 ± 7.2 vs 31.0 ± 9.1, respectively; \( P < 0.001 \)), and AUC >10 mmol/L (0.18 ± 0.27 vs 0.52 ± 0.55 mmol/L per h, respectively; \( P < 0.001 \); Table 2). The linear mixed-effect model analyses of glucose fluctuations demonstrated no sequence or period effects (all \( P > 0.05 \)).

In the subanalysis of drug order, the mean glucose level in both phases was identical in the population receiving mitiglinide/voglibose first (8.18 ± 1.36 vs 8.10 ± 1.80 mmol/L; \( P = 0.838 \)), whereas the population receiving glimepiride first had a lower mean glucose level with mitiglinide/voglibose than with glimepiride (7.70 ± 1.45 vs 8.31 ± 1.60 mmol/L, respectively; \( P = 0.003 \)). The SD of glucose was lower in the mitiglinide/voglibose than in the glimepiride phase, regardless of drug order (mitiglinide/voglibose first: 1.36 ± 0.53 vs 2.17 ± 0.70 mmol/L, respectively [\( P = 0.008 \)]; glimepiride first: 1.23 ± 0.40 vs...
1.97 ± 0.53 mmol/L, respectively \([P < 0.001]\). Hypoglycemia was not observed during treatment with mitiglinide/voglibose, but was observed 0.35 times/day with glimepiride treatment.

Analysis of the MTT results (Table 3) showed higher premeal glucose levels \((P < 0.001)\) and lower post-meal glucose levels at 120 min \((P < 0.001)\) in the mitiglinide/voglibose than glimepiride phase. Although the premeal insulin levels did not differ between the mitiglinide/voglibose and glimepiride phases, the 120-min post-meal insulin level was significantly lower in the mitiglinide/voglibose than glimepiride phase (Table 3). Similarly, although the premeal glucagon levels were almost identical in both the mitiglinide/voglibose and glimepiride phases, the 120-min post-meal glucagon level was slightly higher in the mitiglinide/voglibose than glimepiride phase \(\(P = 0.003; \text{Table 3}\)\).

### Discussion

This study revealed that in patients with T2DM, adding the combination of mitiglinide/voglibose to treatment with a DPP-4 inhibitor resulted in fewer glucose fluctuations than adding glimepiride, even though the mean glucose levels were almost identical in both phases. Furthermore, fewer hypoglycemic episodes were observed with mitiglinide/voglibose than with glimepiride.

The most significant finding of the present study is the effective reduction in glucose fluctuations and hypoglycemic episodes with mitiglinide/voglibose therapy. Postprandial glucose fluctuations induce more oxidative stress than sustained hyperglycemia.\(^{11}\) Moreover, postprandial glucose fluctuations decrease vasodilator responses,\(^{12}\) damage endothelial cells,\(^{13}\) and are associated with cognitive decline\(^ {14}\) in patients with T2DM. Clinically, it has been reported that high glucose fluctuations predict the risk of cardiac events better than HbA1c levels in patients with acute myocardial infarction,\(^ {15}\) although large studies found no relationship between glucose variability and cardiovascular events.\(^ {16,17}\)Colorless studies have demonstrated that glycemic variability is greater in patients who experience hypoglycemia, particularly severe hypoglycemia.\(^ {18,19}\) The CGM data in the present study showed sporadic hypoglycemic episodes with glimepiride therapy despite identical mean glucose levels being obtained with both therapies, suggesting that evaluating patients’ glucose control using only a mean glucose or HbA1c level is inadequate. Hypoglycemia is associated with cardiovascular-related death\(^ {20}\) and dementia,\(^ {21}\) and prolonged hypoglycemia can result in sustained brain damage.

### Table 2  Efficacy measures derived from continuous glucose monitoring

|                         | MV \((n = 20)\) | Glimepiride \((n = 20)\) | Effect size of LS mean difference (95% CI) | \(P\)-value |
|-------------------------|-----------------|--------------------------|------------------------------------------|-------------|
| Mean glucose (mmol/L)   | 8.01 ± 1.33     | 8.24 ± 1.61              | –0.15 (–0.77, 0.47)                      | 0.184       |
| Standard deviation (mmol/L) | 1.30 ± 0.45   | 2.10 ± 0.61              | –1.46 (–2.16, –0.77)                     | <0.001      |
| MAGE (mmol/L)           | 3.47 ± 1.28     | 5.28 ± 2.15              | –1.00 (–1.66, –0.35)                     | <0.001      |
| M-value                 | 24.6 ± 27.2     | 70.0 ± 61.9              | –0.93 (–1.58, –0.28)                     | <0.001      |
| CONGA 1 value           | 22.6 ± 7.2      | 31.0 ± 9.1               | –1.00 (–1.66, –0.35)                     | <0.001      |
| AUC >10 mmol/L (mmol/L per h) | 0.18 ± 0.27   | 0.52 ± 0.55              | –0.77 (–1.41, –0.13)                     | <0.001      |
| Hypoglycemia (no. times/day) | 0             | 0.35                     |                                          |             |

Data are mean ± SD or effect size of the least square (LS) mean differences with bias corrected.

MV, mitiglinide and voglibose; CI, confidence interval; MAGE, mean amplitude of glycemic excursions; CONGA 1, continuous overlapping net glycemic action for a 1-h time interval; AUC, area under the curve.

### Table 3  Changes in metabolic profile during the meal tolerance test

|                         | MV \((n = 20)\) | Glimepiride \((n = 20)\) | Effect size of LS mean difference (95% CI) | \(P\)-value |
|-------------------------|-----------------|--------------------------|------------------------------------------|-------------|
| Glucose (mmol/L)        |                 |                          |                                          |             |
| Premeal                 | 7.53 ± 1.44     | 6.94 ± 1.33              | 0.42 (–0.21, 1.04)                       | <0.001      |
| Post-meal (at 120 min)  | 8.72 ± 1.60     | 12.06 ± 2.94             | –1.38 (–2.07, –0.69)                     | <0.001      |
| Insulin (pmol/L)        |                 |                          |                                          |             |
| Premeal                 | 52.4 ± 18.0     | 56.7 ± 18.0              | –0.23 (–0.86, 0.39)                      | 0.271       |
| Post-meal (at 120 min)  | 267.1 ± 171.6   | 323.1 ± 151.5            | –0.34 (–0.96, 0.29)                      | 0.006       |
| Glucagon (ng/L)         |                 |                          |                                          |             |
| Premeal                 | 86.7 ± 26.7     | 89.9 ± 22.6              | –0.13 (–0.75, 0.49)                      | 0.330       |
| Post-meal (at 120 min)  | 99.6 ± 20.6     | 85.1 ± 21.7              | 0.67 (0.03, 1.31)                        | 0.003       |

Data are mean ± SD or effect size of the least square (LS) mean differences with bias corrected.

MV, mitiglinide and voglibose; CI, confidence interval.
damage. The concept of measuring glucose levels at various meaningful times, in addition to measuring HbA1c levels, should be evaluated.

Sulfonylureas are known to increase the risk of hypoglycemia, especially in patients with renal failure. Prolonged hypoglycemia and consequent weight gain are the most frequent adverse effects of sulfonylureas and are considered major issues. It is conceivable that the higher postprandial glucose levels associated with glimepiride observed in the present study were due to delayed stimulation of insulin secretion, resulting in the observed intermeal hypoglycemia and diurnal glycemic fluctuations. Glinides are insulin secretagogues with a similar mechanism of action to sulfonylureas. In the present study, we used mitiglinide because it has been reported to be safe, even in patients with renal failure. Because of the rapid time to maximum drug concentration and short half-life of glinides, they provoke rapid insulin secretion to reduce the postprandial glucose spike and rarely cause prolonged insulin secretion. In addition, voglibose reduces postprandial hyperglycemia and insulin secretion by delaying the digestion of carbohydrates in the small intestine. Thus, glinides and αGI may have synergistic effects for treating postprandial hyperglycemia and sparing postprandial insulin secretion. This combination is certainly rational because impaired early insulin secretion is the main pathogenesis of T2DM. It may be especially suitable for Asian populations because their insulin secretion is attenuated compared with that of Caucasians, and because the Asian diet includes carbohydrate-rich meals such as polished rice. Furthermore, treating postprandial hyperglycemia with an αGI does not stimulate excess insulin secretion; delayed absorption of glucose may prevent the subsequent premeal hypoglycemia induced by the glinides.

Importantly, mitiglinide/voglibose therapy reduced glucose fluctuations not only in the postprandial period, but also during the course of the entire day. This effect was seen despite its use as an add-on treatment to DPP-4 inhibitor therapy, whose effects of enhancing glucose-dependent insulin secretion and glucagon suppression over the whole day were established. The underlying mechanism for this may be a synergistic effect between αGI and DPP-4 inhibitors. An increase in the amount of undigested food stimulates the lower small intestine and enhances postprandial glucagon-like peptide-1 secretion in patients with T2DM. These findings suggest that αGI therapy is, potentially, the preferred incretin treatment as an add-on to DPP-4 inhibitor therapy. In the present study, the 120-min postprandial plasma glucose levels were significantly lower in patients in the mitiglinide/voglibose than glimepiride phase, with slightly higher glucagon levels and significantly lower insulin levels observed. In addition, an animal study reported that mitiglinide elicits glucagon secretion from α-cells directly. However, the relatively higher postprandial glucagon levels observed with mitiglinide/voglibose may be caused secondary by low postprandial glucose and insulin levels, considering that postprandial glucose changes were less pronounced with mitiglinide/voglibose than with glimepiride.

Although combination therapy with a DPP-4 inhibitor and mitiglinide/voglibose was associated with few glucose excursions and little hypoglycemic risk in the present study, it is unknown whether this therapeutic approach can prevent cardiovascular events in patients with T2DM. The NAVIGATOR (Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research) trial showed that glinides are not effective in decreasing either new-onset diabetes or cardiovascular events in a population at high risk, whereas αGI have the potential to prevent cardiovascular events. It has been reported that mitiglinide decreases oxidative stress and inflammation and improves endothelial function. Although further investigation is required, the combination drug mitiglinide/voglibose has the potential to prevent cardiovascular events.

The strengths of the present study include that it is the first randomized trial using CGM to investigate glucose excursions associated with mitiglinide/voglibose or glimepiride. In addition, we highlighted the risk of hypoglycemia unawareness related to the use of sulfonylureas. However, the present study also has several limitations. First, there was no washout period between each therapy phase (not the CGM period) and the study duration may be short for glimepiride; this is of concern. Moreover, all study participants were inpatients; hence, their glycemic control may have improved sequentially during admission. However, this trial was performed in a real-world medical practice and setting a washout period could bring about the possibility of worsening glucose control, which may affect study results. Furthermore, the linear mixed-effects model analyses of glucose excursion parameters did not demonstrate a carryover or period effect. More than 2 days were provided before each CGM period; this may have avoided the carryover effect and may have provided a duration that allowed the almost maximum effect of glimepiride to be reached. This period also provided more than 5 days for vildagliptin to reach steady state conditions during the CGM period. According to pharmacokinetic and pharmacodynamic data, serum glimepiride reaches its maximum level on the first day of administration, does not accumulate in the serum, and has a half-life of 9 h with multiple doses in patients with T2DM. Its metabolite, which has less than one-third of
the glucose lowering activity of glimepiride itself, has a half-life of a few hours. Although the serum drug level does not always correspond to its effect in vivo, more than 2 days before each CGM period may have been sufficient to provide a reasonably fair comparison between glimepiride and mitiglinide/voglibose. Second, the sample size was small and no long-term evaluation of effectiveness was performed. However, significant differences and benefits of mitiglinide/voglibose were observed despite the small study sample. Trials conducted over a longer period and with a larger number of subjects are needed to further explore this issue. Third, both mitiglinide and voglibose need to be taken immediately before each meal. This may lead to failure in the accurate administration of drugs and may negatively affect adherence to the drugs; we did not consider this in the present study. However, using a fixed-dose combination drug should offer advantages regarding adherence. Motivating patients’ perceptions through education and encouragement may also help resolve this issue.

In conclusion, adding the combination drug mitiglinide/voglibose to vildagliptin resulted in more efficient postprandial glucose control and no hypoglycemic episodes compared with the addition of glimepiride. Improvements in postprandial hyperglycemia may be crucial for preventing cardiovascular events. The therapeutic option of mitiglinide/voglibose as an add-on to vildagliptin therapy is considered suitable for achieving ideal and careful glycemic control.

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Disclosure

None of the authors have any potential conflicts of interest to declare associated with this research.

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