Improved time in range and postprandial hyperglycemia with canagliflozin in combination with teneligliptin: Secondary analyses of the CALMER study

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Keywords
Post-prandial blood glucose, Sodium–glucose cotransporter 2 inhibitor, Time in range

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ABSTRACT
Aims/Introduction: We recently reported the beneficial effect of the combination of sodium–glucose cotransporter 2 inhibitor and dipeptidyl peptidase-4 inhibitor on daily glycemic variability in patients with type 2 diabetes mellitus. Additional favorable effects of combination therapy were explored in this secondary analysis.

Materials and Methods: The CALMER study was a multicenter, open-label, prospective, randomized, parallel-group comparison trial for type 2 diabetes mellitus involving continuous glucose monitoring under meal tolerance tests. Patients were randomly assigned to switch from teneligliptin to canagliflozin (SWITCH group) or to add canagliflozin to teneligliptin (COMB group). The continuous glucose monitoring metrics, including time in target range, were investigated.

Results: All 99 participants (mean age 62.3 years; mean glycated hemoglobin 7.4%) completed the trial. The time in target range was increased in the COMB group (71.2–82.7%, P < 0.001). The extent of the reduction in time above target range was significantly larger in the COMB group compared with the SWITCH group (-14.8% vs -7.5%, P < 0.01). Area under the curve values for glucose at 120 min after all meal tolerance tests were significantly decreased in the COMB group compared with the SWITCH group (P < 0.05).

Conclusions: Sodium–glucose cotransporter 2 inhibitor combined with dipeptidyl peptidase-4 inhibitor improved the quality of glycemic variability and reduced postprandial hyperglycemia compared with each monotherapy.

INTRODUCTION
A goal for treatment of patients with type 2 diabetes mellitus is to prevent the development of diabetic complications by bringing their blood glucose level as close to normal as possible. Although glycated hemoglobin (HbA1c) has been recognized as a marker of diabetic complications for many years, it does not exactly reflect daily glycemic variability, postprandial hyperglycemia and hypoglycemia1,2. Previous studies showed that minimization of glucose variability reduced the frequency of cardiovascular events and dementia3,4. Postprandial hyperglycemia is also a well-known risk factor of the onset and progress of microvascular and macrovascular complications5. Continuous glucose monitoring (CGM) systems have been investigated, and are currently the most suitable devices for
evaluating daily glycemic variability, postprandial hyperglycemia and asymptomatic hypoglycemia in clinical practice.

The addition of a DPP-4 inhibitor (DPP-4i) or a sodium–glucose cotransporter 2 inhibitor (SGLT2i) to type 2 diabetes mellitus treatments was reported to show benefits in improving daily glycemic variability. We recently reported, in the CALMER study, that DPP-4i-SGLT2i combination therapy had synergetic effects on reducing the mean amplitude of glycemic excursions, as the primary outcome, without increasing hypo-
glycemia. Today, the concept of time ranges (TRs) has been well
recognized in glycemic control. Several previous studies showed time in target range (TIR) had a strong correlation with diabetic complications.

In the present study, we carried out secondary analyses of the CALMER study to investigate the merits of combination therapy with DPP-4i and SGLT2i by evaluating various CGM metrics other than mean amplitude of glycemic excursions, with a particular focus on TIR and postprandial hyperglycemia.

MATERIAL AND METHODS

Study overview

The present study comprised secondary analyses of the CALMER study, a multicenter (10 sites), open-label, prospective, randomized, parallel-group comparison trial using CGM and meal tolerance tests (MTTs) involving four consecutive meals (dinner, breakfast, lunch and dinner). All patients provided written informed consent before enrollment. The rationale and protocol of the CALMER study were described elsewhere, and the full list of inclusion and exclusion criteria is provided in Data S1. Briefly, eligible participants included patients with type 2 diabetes mellitus, aged 20–80 years, HbA1c of 6.5–9.0%, body mass index (BMI) of ≥23 kg/m², estimated glomerular filtration rate of ≥45 ml/min/1.73 m² and treatment with teneligliptin 20 mg/day for >12 weeks. All participants who met the criteria for enrollment were randomly assigned (1:1) to switch from teneligliptin 20 mg/day to canagliflozin 100 mg/day (SWITCH group) or to add canagliflozin 100 mg/day to teneligliptin 20 mg/day (COMB group), followed by 14 days of CGM. Allocation factors included age, BMI, HbA1c and estimated glomerular filtration rate. After performance of the first MTT while the patients were taking teneligliptin, the allocated medication was started in each group. After 7 days, the second identical MTT was carried out. For MTTs, we prepared the frozen food dish and several sides of packed rice (100, 130 and 200 g/meal) according to BMI. The total calorie intake was set to 30–35 kcal/participant’s ideal bodyweight (height [m²] × 22 kg)/day, and its carbohydrate ratio was approximately 50–65%. Participants were asked to maintain their lifestyle as similar as possible between the first and second MTTs. The CALMER study was registered with the University Hospital Medical Information Network (UMIN) Center Clinical Trials Registry (UMIN000029628), and protocol was approved by the institutional review board at Hokkaido University Hospital Clinical Research and Medical Innovation Center (017-0037), and it was carried out in accordance with the Declaration of Helsinki and its amendments.

In this analysis, we did not include the first dinner in the analyses, and thus used 24-h data including three consecutive meals (breakfast, lunch and dinner). The outcomes for the secondary efficacy end-points were designed before starting the original study. The changes in percentages of time per day in target glucose range (70–180 mg/dL; TIR), time per day below target range (<70 mg/dL; TBR), time per day above target range (≥180 mg/dL; TAR) and mean blood glucose (MBG) were investigated as core CGM metrics. The differences between pre-prandial and 120 min post-prandial glucose levels (Δ0–120) and the area under the curve values during 0–120 min (AUC 0–120) were analyzed for each meal during the MMTs.

Statistical analysis

Differences in the baseline characteristics between the two groups were evaluated by ANCOVA for continuous variables, and by a χ²-test or Fisher’s exact test for categorical variables. Correlations were evaluated by Spearman’s rank-order correlation analysis. Logistic regression models were applied to identify factors independently associated with the rise of TIR in the COMB group, and a receiver operating characteristic curve analysis was used to define the cut-off values. Multiple regression analysis was used to determine predictors for the change in AUC (AAUC). The results within each group were compared by a paired-sample t-test or the Wilcoxon signed-rank test.

RESULTS

A total of 99 patients were randomly assigned either to the SWITCH group (n = 48) or to the COMB group (n = 51), and all participants completed the study. The baseline charac-
teristics of the study participants have already been reported. Briefly, 61.6% of patients were men, the mean age was 62.3 years, mean BMI was 26.3 kg/m², mean HbA1c was 7.4% (57.0 mmol/mol) and 49 patients used sulfonylurea or insulin.

As shown in Table 1, MBG and TAR were significantly decreased in both groups, and the extents of the reductions were significantly larger in the COMB group compared with the SWITCH group (MBG: COMB, −22.3 mg/dL [143.9 ± 28.7 to 121.6 ± 26.1 mg/dL] vs SWITCH, −10.6 mg/dL [148.1 ± 27.0 to 137.5 ± 23.0 mg/dL], P < 0.01; TAR: COMB, −14.8% (26.5–11.6%) vs SWITCH, –7.5% (26.8–19.3%), P < 0.01). Meanwhile, TIR and TBR were significantly increased in both groups, but the extents of the increases did not differ significantly between the two groups (TIR: COMB, +11.5% [71.2–82.7%] vs SWITCH, +5.8% [72.5–78.3%], P = 0.09; TBR: COMB, +3.3% [2.4–5.7%] vs SWITCH, +1.7% [0.8–2.5%], P = 0.13). TRs <54 mg/dL (%) were rare and comparable between the groups (COMB 0.1–0.4% vs SWITCH 0.0–
When the postprandial hyperglycemia at individual meals was considered separately (Figure 1), the AUC 0–120 values for all meals were significantly decreased in the second MTT compared with the first MTT in the COMB group (breakfast 401.1 ± 100.4 to 326.4 ± 82.6 mg/dL h, \(P < 0.001\); lunch 325.3 ± 92.6 to 278.0 ± 65.3 mg/dL h, \(P < 0.001\); dinner 329.4 ± 91.4 to 285.8 ± 90.9 mg/dL h, \(P < 0.001\)), whereas the AUC 0–120 value at breakfast only was decreased in the SWITCH group (384.5 ± 91.2 to 344.1 ± 91.4 mg/dL h, \(P < 0.01\)). The decrease in the COMB group was greatly superior to that in the SWITCH group (\(P < 0.05\); Table 3, Figure 2). When postprandial hyperglycemia was analyzed using the Δ0–120 values, similar tendencies to the AUC 0–120 values were seen in both groups, although the improvement in Δ0–120 values did not reach statistical significance for lunch in the COMB group (Table 4).

**DISCUSSION**

The present analyses showed beneficial effects of the combination of teneligliptin and canagliflozin on two distinctive features: TRs and postprandial glycemic excursions. TRs are currently used for assessment of glycemic control in patients with diabetes, with TIR >70% and TAR <25% recommended as an international consensus in 2019 [10,11]. In the present study, the combination therapy increased the mean TIR to 82.7% (+11.5%) and the achievement rate of TIR >70% was increased from 58.0 to 79.2% by adding canagliflozin to teneligliptin. Increases in TIR contribute to a decline in diabetic complications, at least for some classical microvascular complications and atherosclerosis [12–15], because TIR is determined by not only the average glycemic control, but also the extent and magnitude of hyperglycemia [16]. Furthermore, 10% improvement in TIR...
was identified as a useful indicator for preventing diabetic complications\(^\text{15,17}\). TIR was increased by >10% in the COMB group, meaning that the combination therapy could be one of the promising therapies for comprehensive control of diabetic complications. We showed in a logistic regression analysis that MBG was a key characteristic predicting the improvement of TIR in the combination therapy (Table 2). It indicates that adding SGLT2i to DPP-4i in type 2 diabetes mellitus patients with a higher level of baseline MBG might lead to greater effects on increasing TIR. The combination therapy could be a crucial strategy for patients with type 2 diabetes mellitus who are at high risk of diabetic complications.

For strict glycemic control, appropriate reduction of insulin or sulfonylurea should be always considered\(^\text{18}\). The combination therapy slightly, but significantly, increased TBR (2.4–5.7%) in the COMB group, although the group difference was not significant and the TRs <54 mg/dL were not increased. Because glycemic variability is a significant and independent determinant of hypoglycemia in patients with type 2 diabetes mellitus on insulin therapy\(^\text{19}\), once the dose of insulin or sulfonylurea has been adjusted appropriately, TBR should be rather decreased by the combination therapy through improving glycemic variability\(^\text{9}\). Previous studies showed that CGM values were lower than self-monitoring blood glucose values in the low glucose range\(^\text{20}\), and that capillary and venous glucose concentrations can differ under dynamic conditions\(^\text{21}\). Therefore, CGM data might not be highly accurate and the possibility of such inaccuracies should be considered, especially in the low glucose region.

The combination therapy showed marked improvement of postprandial hyperglycemia in the present study. Previous studies showed that postprandial hyperglycemia was associated with an increased risk of death\(^\text{22,23}\), and was an independent factor for arteriosclerosis and cardiovascular events\(^\text{24}\). Postprandial hyperglycemia induced oxidative stress\(^\text{25}\), decreased vasodilator response\(^\text{26}\) and damaged endothelial cells\(^\text{27}\). We previously

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**Table 3** | Comparisons of the area under the curve values for glucose at 120 min after meal tolerance tests between the groups

|        | First MTT       | Second MTT      | P       |
|--------|-----------------|-----------------|---------|
| **Breakfast** |                 |                 |         |
| SWITCH (mg/dL h) | 3845 ± 91.2   | 3441 ± 91.4***  | <0.05   |
| COMB (mg/dL h)   | 401.1 ± 100.4  | 326.4 ± 82.6*** |         |
| **Lunch**       |                 |                 |         |
| SWITCH (mg/dL h) | 3346 ± 97.9    | 320.5 ± 72.5    | <0.05   |
| COMB (mg/dL h)   | 325.3 ± 92.6   | 278.0 ± 65.3*** |         |
| **Dinner**      |                 |                 |         |
| SWITCH (mg/dL h) | 3374 ± 99.1    | 331.1 ± 75.9    | <0.05   |
| COMB (mg/dL h)   | 329.4 ± 91.4   | 285.8 ± 90.9*** |         |

Values are presented as the mean ± standard deviation. The P-values were calculated for the differences in area under the curve values between the switched from teneligliptin to canagliflozin (SWITCH) group and the added canagliflozin to teneligliptin (COMB) group (ANCOVA). ***P < 0.01, ****P < 0.001 during first meal tolerance test (MTT) and second MTT (paired-sample t-test).

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**Figure 1** | Blood glucose concentrations during meal tolerance tests (MTTs). Dashed lines indicate the data at the first MTT while taking teneligliptin. Solid lines indicate the data at the second MTT. Grey lines indicate the group that switched from teneligliptin to canagliflozin (SWITCH). Black lines indicate the group that added canagliflozin to teneligliptin (COMB). BG, blood glucose.
described several possible mechanisms for the synergistic effects of the combination therapy on reducing glycemic variability, including complementary effects on pancreatic α- and β-cell functions, and decreasing soluble DPP-4. These mechanisms would be likewise included in the decrease of postprandial blood glucose elevation by the combination therapy.

The improvement in lowering post-prandial hyperglycemia was especially highlighted at breakfast. The glucose-lowering effect of incretin is diminished in the hyperglycemic state and can be improved by lowering the plasma glucose level. SGLT2i effectively decreases the fasting plasma glucose level, thereby restoring the DPP-4i effect, especially after breakfast in the combination therapy. However, the post-prandial hyperglycemia (AUC 0–120) at breakfast was also significantly lowered in the SWITCH group. Therefore, other additional mechanisms might be involved in its improvement. Canagliflozin has a different characteristic from other SGLT2i. It inhibits SGLT2 in the kidney, as the other SGLT2is do, but also partially inhibits SGLT1 in the intestinal tract and pancreatic α-cells. The combination therapy of canagliflozin and DPP-4i increased plasma GLP-1 levels and improved glucose excursions in diabetic fatty rats. In a randomized controlled trial, canagliflozin provided smaller postprandial plasma glucose excursions than dapagliflozin. Furthermore, in likely support for the hypothesis of partial SGLT1 inhibition in the intestinal tract with canagliflozin, no significant differences were found for the success of glycemic control in the Diversity-CVR study, which compared dapagliflozin with DPP-4i.

Furthermore, in this analysis, pre-prandial hyperglycemia was improved, as well as post-prandial hyperglycemia, in the COMB group. It is well known that alpha-glucosidase inhibitors and glinide acting directly on postprandial hyperglycemia also improved pre-prandial hyperglycemia. DPP-4 inhibitors that improved postprandial hyperglycemia on glycemic responsiveness also improve the next pre-prandial glucose level. It is important to ensure control of postprandial hyperglycemia and not carry it over to the next pre-prandial. The strong interaction of the combination therapy in the COMB group had a positive effect on both pre-prandial glucose levels and postprandial glucose, and improved glycemic variability.

There were several limitations to the present study. First, the trial had an open-label design, which might have contributed to bias. Second, the study duration for the analysis was short. Because fat mass reduction would be sustained for more than a few months after starting SGLT2i, the results for CGM metrics might be clearer after long-term use of SGLT2i. However, SGLT2i can rapidly relieve glucose toxicity, and its glycemic effects should be seen relatively earlier than those of other oral hypoglycemic agents. Furthermore, previous studies showed that CGM during the most recent 14 days was strongly correlated with long-term mean glucose, time in TRs and hyperglycemia metrics. Therefore, we decided on a shorter observation period to reduce the influence of various other external factors on blood glucose fluctuations, and maintain higher quality of the data in a randomized control style using MTTs.

In conclusion, SGLT2i combined with DPP-4i improved the quality of glycemic variability and reduced post-prandial hyperglycemia compared with each monotherapy.
### Table 4

| Time (min) | First MTT | Second MTT |
|------------|-----------|------------|
|            | P         | (ΔΔ-120)   |
| 0          | 0.6       | 0.7        |
| 120        | <0.05     | <0.05      |

Values are presented as the mean ± standard deviation. The P(A–120)-values were calculated for the changes from 0 to 120 min (ΔΔ-120) during the first meal tolerance test (MTT), baseline, and the added canagliflozin to teneligliptin (COMB) group and the added canagliflozin to teneligliptin (SWITCH) group (ANCOVA).

#### DISCLOSURE

A Nakamura, S Taneda, Y Kurihara, T Atsumi and H Miyoshi received honoraria for lectures and received research funding from some organizations as follows. A Nakamura received research funding from Mitsubishi Tanabe Pharma Co. and Ono Pharmaceutical Co., Ltd. S Taneda received honoraria for lectures from Takeda Pharmaceutical Co., Ltd. and Novo Nordisk Pharma Ltd. Y Kurihara received honoraria for lectures from Astellas Pharma Inc., AstraZeneca, Mitsubishi Tanabe Pharma Co., MSD K.K., Ono Pharmaceutical Co., Ltd., Sanofi, Shionogi & Co., Ltd., Taisho Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd. T Atsumi received honoraria for lectures from Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Pfizer Inc., AbbVie Inc., Eisai Co. Ltd., Daiichi Sankyo Co., Bristol-Myers Squibb Co., UCB Japan Co. Ltd. and Eli Lilly Japan K.K., and received research funding from Astellas Pharma Inc., Takeda Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Co., Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Otsuka Pharmaceutical Co., Ltd., Pfizer Inc. and Alexion Inc. H Miyoshi received honoraria for lectures from Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., MSD K.K., Novartis Pharma, Novo Nordisk Pharma Ltd., Kowa Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co, Ono Pharmaceutical Co., Ltd. and Sanofi, and received research funding from Astellas Pharma Inc., Daiichi Sankyo Co., Otsuka Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Sumitomo Dainippon Pharma Co. Ltd., Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Co., Novo Nordisk Pharma, Kowa Pharmaceutical Co., Ltd., Abbott Japan Co., Nippon Boehringer Ingelheim Co, Ono Pharmaceutical Co., Ltd. and Taisho Pharmaceutical Co., Ltd. The other authors declare no conflict of interest.

#### REFERENCES

1. Cox DJ, Kovatchev BP, Julian DM, et al. Frequency of severe hypoglycemia in insulin-dependent diabetes mellitus can be predicted from self-monitoring blood glucose data. *J Clin Endocrinol Metab* 1994; 79: 1659–1662.

2. Qu Y, Jacober SJ, Zhang Q, et al. Rate of hypoglycemia in insulin-treated patients with type 2 diabetes can be predicted from glycemic variability data. *Diabetes Technol Ther* 2012; 14: 1008–1012.

3. Mendez CE, Ki M, Ata A, et al. Increased glycemic variability is independently associated with length of stay and mortality in noncritically ill hospitalized patients. *Diabetes Care* 2013; 36: 4091–4097.
4. Cui X, Abduljallil A, Manor BD, et al. Multi-scale glycemic variability: a link to gray matter atrophy and cognitive decline in type 2 diabetes. *PloS One* 2014; 9: e86284.

5. Avogaro A. Postprandial glucose: marker or risk factor? *Diabetes Care* 2011; 34: 2333–2335.

6. Nathan DM, Kuenen J, Borg R, et al. Translating the A1C assay into estimated average glucose values. *Diabetes Care* 2008; 31: 1473–1478.

7. Mondick J, Riggs M, Sasaki T, et al. Mixed-effects modelling to quantify the effect of empagliflozin on renal glucose reabsorption in patients with type 2 diabetes. *Diabetes Obes Metab* 2016; 18: 241–248.

8. Nomoto H, Miyoshi H, Sugawara H, et al. A randomized controlled trial comparing the effects of dapagliflozin and DPP-4 inhibitors on glucose variability and metabolic parameters in patients with type 2 diabetes mellitus on insulin. *Diabetol Metab Syndr* 2017; 9: 54.

9. Cho KY, Nomoto H, Nakamura A, et al. Favourable effect of the sodium-glucose co-transporter-2 inhibitor canagliflozin plus the dipeptidyl peptidase-4 inhibitor teneligliptin in combination on glycaemic fluctuation: an open-label, prospective, randomized, parallel-group comparison trial (the CALMER study). *Diabetes Obes Metab* 2020; 22: 458–462.

10. Battelino T, Danne T, Bergenstal RM, et al. Clinical targets for continuous glucose monitoring data interpretation: recommendations from the international consensus on time in range. *Diabetes Care* 2019; 42: 1593–1603.

11. American Diabetes Association. Glycemic targets: standards of medical care in diabetes—2020. *Diabetes Care* 2020; 43: S66–S76.

12. Lu J, Ma X, Zhou J, et al. Association of time in range, as assessed by continuous glucose monitoring, with diabetic retinopathy in type 2 diabetes. *Diabetes Care* 2018; 41: 2370–2376.

13. Mayeda L, Katz R, Ahmad I, et al. Glucose time in range and peripheral neuropathy in type 2 diabetes mellitus and chronic kidney disease. *BMJ Open Diabetes Res Care* 2020; 8: e000991.

14. Yoo JH, Choi MS, Ahn J, et al. Association between continuous glucose monitoring-derived time in range, other core metrics, and albuminuria in type 2 diabetes. *Diabetes Technol Ther* 2020; 22: 768–776.

15. Lu J, Ma X, Shen Y, et al. Time in range is associated with carotid intima-media thickness in type 2 diabetes. *Diabetes Technol Ther* 2020; 22: 72–78.

16. Advani A. Positioning time in range in diabetes management. *Diabetologia* 2020; 63: 242–252.

17. Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. *Diabetes Care* 2019; 42: 400–405.

18. Committee on the Proper Use of SGLT2 Inhibitors. Recommendations on the proper use of SGLT2 inhibitors. *J Diabetes Investig* 2020; 11: 257–261.

19. Uemura F, Okada Y, Torimoto K, et al. Relation between hypoglycemia and glycemic variability in type 2 diabetes patients with insulin therapy: a study based on continuous glucose monitoring. *Diabetes Technol Ther* 2018; 20: 140–146.

20. Babaya N, Noso S, Hiromine Y, et al. Flash glucose monitoring in type 1 diabetes: a comparison with self-monitoring blood glucose. *J Diabetes Investig* 2020; 11: 1222–1229.

21. Kempe K, Price D, Ellison J, et al. Capillary and venous blood glucose concentrations measured during intravenous insulin and glucose infusion: a comparison of steady and dynamic states. *Diabetes Technol Ther* 2009; 11: 669–674.

22. The DECODE Study Group on behalf of the Europe An Diabetes Epidemiology Group. Glycose Tolerance and Mortality: Comparison of WHO and American Diabetes Association Diagnostic Criteria. The DECODE Study Group. European Diabetes Epidemiology Group. Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe. *Lancet* 1999; 354: 617–621.

23. Qiao Q, Nakagami T, Tuomilehto J. Comparison of the fasting and the 2-h glucose criteria for diabetes in different Asian cohorts. *Diabetologia* 2000; 43: 1470–1475.

24. Nakagami T, the DECODA Study Group. Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. *Diabetologia* 2004; 47: 385–394.

25. Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycaemia in patients with type 2 diabetes. *JAMA* 2006; 295: 1681–1687.

26. Williams SB, Goldfine AB, Tirzimi FK, et al. Acute hyperglycaemia attenuates endothelium-dependent vasodilatation in humans in vivo. *Circulation* 1998; 97: 1695–1701.

27. Esposito K, Ciotola M, Carleo D, et al. Post-meal glucose peaks at home associate with carotid intima-media thickness in type 2 diabetes. *J Clin Endocrinol Metab* 2008; 93: 1345–1350.

28. Forst T, Falk A, Andersen G, et al. Effects on α- and β-cell function of sequentially adding empagliflozin and linagliptin to therapy in people with type 2 diabetes previously receiving metformin: an exploratory mechanistic study. *Diabetes Obes Metab* 2017; 19: 489–495.

29. Ahn CH, Oh TJ, Kwak SH, et al. Sodium-glucose cotransporter-2 inhibition improves incretin sensitivity of pancreatic β-cells in people with type 2 diabetes. *Diabetes Obes Metab* 2018; 20: 370–377.

30. Aso Y, Kato K, Sakurai S, et al. Impact of dapagliflozin, an SGLT2 inhibitor, on serum levels of soluble dipeptidyl peptidase-4 in patients with type 2 diabetes and non-alcoholic fatty liver disease. *Int J Clin Pract* 2019; 73(S): e13335.
31. Meier JJ, Nauck MA. Is the diminished incretin effect in type 2 diabetes just an epiphenomenon of impaired beta-cell function? Diabetes 2010; 59: 1117–1125.
32. Oguma T, Nakayama K, Kuriyama C, et al. Intestinal sodium glucose cotransporter 1 inhibition enhances glucagon-like peptide-1 secretion in normal and diabetic rodents. J Pharmacol Exp Ther 2015; 354: 279–289.
33. Suga T, Kikuchi O, Kobayashi M, et al. SGLT1 in pancreatic α cells regulates glucagon secretion in mice, possibly explaining the distinct effects of SGLT2 inhibitors on plasma glucagon levels. Mol Metab 2019; 19: 1–12.
34. Sha S, Polidori D, Farrell K. Pharmacodynamic differences between canagliflozin and dapagliflozin: results of a randomized, double-blind, crossover study. Diabetes Obes Metab 2015; 17: 188–197.
35. Fuchigami A, Shigiyama F, Kitazawa T, et al. Efficacy of dapagliflozin versus sitagliptin on cardiometabolic risk factors in Japanese patients with type 2 diabetes: a prospective, randomized study (DIVERSITY-CVR). Cardiovasc Diabetol 2020; 19: 1.
36. Kasthuri S, Poongothai S, Anjana RM, et al. Comparison of glycemic excursion using flash continuous glucose monitoring in patients with type 2 diabetes mellitus before and after treatment with Voglibose. Diabetes Technol Ther 2020. https://doi.org/10.1089/dia.2019.0484
37. Ihana N, Tujimoto T, Yamashita-Honda R, et al. Improvement of both fasting and postprandial glycemic control by the two-step addition of miglitol and mitiglinide to basal insulin therapy: a pilot study. Diabetol Metab Syndr 2014; 6: 48.
38. Tura A, Famgren J, Schweizer A, et al. Four-point preprandial self-monitoring of blood glucose for the assessment of glycemic control and variability in patients with type 2 diabetes treated with insulin and vildagliptin. Int J Endocrinol 2015; 2015: 1–7.
39. Yamamoto C, Miyoshi H, Ono K, et al. Ipragliflozin effectively reduced visceral fat in Japanese patients with type 2 diabetes under adequate diet therapy. Endocr J 2016; 63: 589–596.
40. Ferrannini E, Muscelli E, Frascerra S, et al. Metabolic response to sodium-glucose cotransporter 2 inhibition in type 2 diabetic patients. J Clin Invest 2014; 124: 499–508.
41. Xing D, Kollman C, Beck RW, et al. Optimal sampling intervals to assess long-term glycemic control using continuous glucose monitoring. Diabetes Technol Ther 2011; 13: 351–358.
42. Riddlesworth TD, Beck RW, Gal RL, et al. Optimal sampling duration for continuous glucose monitoring to determine long-term glycemic control. Diabetes Technol Ther 2018; 20: 314–316.

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

Data S1 | Criteria for inclusion and exclusion.