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【 REVIEW ARTICLE 】

# Significance of Glycemic Variability in Diabetes Mellitus

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**Abstract:**
The goal of diabetes treatment is to maintain good glycemic control, prevent the development and progression of diabetic complications, and ensure the same quality of life and life expectancy as healthy people. Hemoglobin A1c (HbA1c) is used as an index of glycemic control, but strict glycemic control using HbA1c as an index may lead to severe hypoglycemia and cardiovascular death. Glycemic variability (GV), such as excessive hyperglycemia and hypoglycemia, is associated with diabetic vascular complications and has been recognized as an important index of glycemic control. Here, we reviewed the definition and evaluated the clinical usefulness of GV, and its relationship with diabetic complications and therapeutic strategies to reduce GV.

**Key words:** glycemic variability, time in range, continuous glucose monitoring, diabetic microvascular complications, diabetic macrovascular complications

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## Introduction

The purpose of diabetes treatment is to maintain good glycemic control from the early stage of diabetes and to prevent the onset and progression of diabetic microvascular complications and arteriosclerotic diseases (1). For this purpose, understanding the status of glycemic control in patients is necessary, and hemoglobin A1c (HbA1c) has been used as a golden standard index of glycemic control. HbA1c is the most commonly used method for evaluating blood glucose control in clinical treatment and is recognized as the key surrogate marker for the development of diabetic complications. In fact, previous studies have revealed that achieving good glycemic control is associated with a lower incidence and lower progression of diabetic microvascular complications, while HbA1c is used as an indicator of glycemic control (2, 3). Subsequently, however, it was reported that strict glycemic control using HbA1c as an index does not lead to the suppression of cardiovascular disease (CVD), but rather to severe hypoglycemia, weight gain, and potentially increased cardiovascular death (4-7).

Although HbA1c represents the mean blood glucose levels over the past 1-3 months, it does not necessarily represent glycemic fluctuations, such as excessive daily hyperglycemia or hypoglycemia (7-10). Self-monitoring of blood glucose (SMBG) has been used to evaluate the status of daily glycemic control; however, SMBG can only evaluate the blood glucose levels at the time of measurement and cannot sufficiently evaluate hypoglycemia and hyperglycemia. Continuous glucose monitoring (CGM) provides a more detailed assessment of daily glycemic control than SMBG because it continuously measures glucose concentrations in the subcutaneous interstitium fluid. With the advancement of CGM technology, CGM has recently been used more and more frequently in clinical practice.

Recently, it has been reported that high glycemic variability (GV) is associated with the development and progression of diabetic vascular complications, the exacerbation of hypoglycemic risk, and the deterioration of patient quality of life (QOL) (11-17). Moreover, GV is now recognized as an important index of glycemic control. This article outlines the significance of GV in diabetes mellitus.

## 1. Definition of GV

GV is usually defined by measuring fluctuations of glucose or other parameters related to glucose homoeostasis within a given time interval (17, 18). There are two types of GV: (i) long-term GV assessed by HbA1c and long-term

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**Table 1. Glycemic Variability Metrics and Time in Ranges.**

| GV metrics | Definition and interpretation | Ref |
|---|---|---|
| A. Long-term GV | | |
| a. SD | Variation from the mean of HbA1c and BG between sequential visits. | 18 |
| b. CV | Magnitude of variability relative to mean HbA1c and BG between sequential visits. | 18 |
| B. Short-term GV | | |
| a. SD | Variation from the mean blood glucose. SD is easy to calculate and is the most used index of within-day GV. SD is highly influenced by the mean blood glucose. SD reflects within-day GV. | 19 |
| b. CV | Magnitude of variability relative to mean blood glucose. CV is calculated by dividing the SD by mean blood glucose and multiplying by 100 to get a percentage. CV reflects within-day GV. | 20 |
| c. MAGE | Average of absolute differences between glucose peaks and nadirs (each difference need to be greater than 1 SD from the mean). MAGE reflects within-day GV. | 21 |
| d. CONGA | SD of differences between a current blood glucose reading and a reading taken hours earlier. CONGA reflects within-day temporal GV. | 22 |
| e. LBGI/HBGI | Calculated by performing a logarithmic transformation to balance the amplitude of hypoglycemic and hyperglycemic ranges. LBGI and HBGI are indices for specific prediction of hypo- and hyperglycemia. | 23, 24 |
| f. ADRR | Sum of the daily peak risks for hypo- and hyperglycemia. ADRR is a risk indicator for both future extreme hypoglycemia and hyperglycemia. | 25 |
| g. MODD | Mean of all valid absolute value differences between two glucose values measured at the same time within a 24-hour interval. MODD reflects between-day GV. | 26 |
| h. IQR of AGP | The spread of glucose data at given timepoints over several sequential days. IQR of AGP reflects the presence of day-to-day synchrony in glucose measures at a given time. | 27 |
| C. Time in ranges | | |
| a. TIR | Percentage of time spent within the target glucose range during the measurement period. TIR is known to be appropriate and useful as clinical targets and outcome measurements that complement HbA1c. | 27 |

GV: glycemic variability, SD: standard deviation, HbA1c: hemoglobin A1c, BG: blood glucose, CV: coefficient of variation, MAGE: mean amplitude of glycemic excursion, CONGA: continuous overlapping net glycemic action, LBGI: low blood glucose index, HBGI: high blood glucose index, ADRR: average daily risk range, MODD: mean of daily differences, IQR: interquartile range, AGP: ambulatory glucose profile, TIR: time in range

fasting and postprandial blood glucose levels; and (ii) short-term GV based on the intraday and interday variability in blood glucose (18, 19). Typical GV indices are shown in Table 1.

### Long-term GV

Long-term GV is a measure of GV after several weeks or months and is assessed by HbA1c or fasting and postprandial blood glucose levels (18, 19). The variation in HbA1c and blood glucose levels between visits is often calculated using the standard deviation (SD) or coefficient of variation (CV) (18, 19). Variations in HbA1c are reported to be correlated with the mean blood glucose and HbA1c levels (28), and some studies have investigated this using methods such as variation independent of the mean (VIM) to eliminate the influence of mean values (31, 32).

### Short-term GV

Short-term GV is an index of within-day and between-day glycemic fluctuations. Recently, short-term GV is more often evaluated by CGM than by SMBG. The SD is a typical index of short-term GV. Although the SD is easy to calculate, it has the disadvantage that it is easily affected by the mean glucose level. The CV is calculated from the SD and mean blood glucose and is recommended as a GV index for the ambulatory glucose profile (AGP) because of its relative sensitivity to hypoglycemia and ease of calculation in comparison to the SD (27).

The mean amplitude of glycemic excursion (MAGE) is often used as another short-term GV index (21). The MAGE focuses on the range of blood glucose levels from nadir to peak and does not evaluate the time from nadir to peak (33). In addition, not all blood glucose fluctuation is evaluated because only blood glucose fluctuation exceeding 1 SD from the mean is evaluated (34). Other GV indices include the J-index, which is calculated from the mean blood glucose and SD (35); the low blood glucose index/high blood glucose index, which is designed to be sensitive to the frequency and severity of hypoglycemia or hyperglycemia (23, 24); and the average daily risk range, which is designed to predict both severe hyperglycemia and hypoglycemia (25).

The mean of daily differences (MODD) is often used as a between-day GV index (26). The MODD is the absolute difference in blood glucose levels at the same time on consecutive days but is easily affected by the content and time of meals. The AGP is used in daily practice using CGM (27). In the AGP, a curve showing the median blood glucose levels and a curve showing the 25th and 75th percentiles of blood glucose levels within a specified period, called the interquartile range (IQR), are drawn. The median, IQR, and other values obtained using the AGP can be used to evaluate within-day and between-day glycemic fluctuations (36).

### Time in range (TIR)

The International Consensus Report on Clinical Targets for Continuous Glucose Monitoring Data Interpretation has been developed and is widely recognized (27). This consen-

sus statement mentioned that the TIR is appropriate and useful as a clinical target and outcome measurement that complements HbA1c for various patients with diabetes (27). Although the TIR is not strictly a GV index, because it indicates the time spent in the target range (usually 70-180 mg/dL), we reported that the TIR and GV are correlated with each other (37). Moreover, the TIR has been reported to be associated with diabetic complications (38-42).

## 2. Mechanisms by Which GV Affects the Development and Progression of Diabetic Complications

The pathogenic mechanisms of diabetic microvascular complications include (i) increased metabolism of the polyol pathway, (ii) increased formation of advanced glycation end-products, (iii) activation of protein kinase C (PKC), and (iv) activation of the hexosamine pathway (42, 43), among others. In addition to hyperglycemia, GV increases reactive oxygen species (ROS) production (44-47), and the aforementioned pathogenic mechanisms (i.e., i-iv) are activated by ROS (43). In fact, the inhibition of mitochondrial superoxide production is reported to suppress polyol metabolism, PKC activation, and hexosamine pathway activation (43). In addition, the risk of hypoglycemia may increase with increasing GV (19, 47, 48), and hypoglycemia also induces oxidative stress (49, 50). Thus, hyperglycemia, rapid changes in blood glucose levels, and hypoglycemia may be involved in the development and progression of diabetic microvascular complications through increased oxidative stress.

Although vascular endothelial dysfunction is an important early indicator of atherosclerotic disease, oxidative stress is also a key player in vascular endothelial dysfunction. In basic experiments, ROS overproduction and increased apoptosis of endothelial cells occur when human umbilical vein endothelial cells are cultured at alternating high and normal glucose concentrations in comparison to when they are cultured at sustained high glucose concentrations (45). Oscillating glucose levels exacerbate oxidative stress and the vascular endothelial function more than constant high glucose levels in patients with type 2 diabetes mellitus (T2DM) (51). In addition, hyperglycemia and GV-induced oxidative stress decrease the activity of nitric oxide synthase and cause dysfunction of the vascular endothelium (52). Furthermore, hypoglycemia not only induces oxidative stress but also leads to vascular endothelial dysfunction by decreasing the bioavailability of nitric oxide in vascular endothelial cells (53) and activating adhesion molecules, such as intercellular adhesion molecule and platelets (54, 55). In addition, the sympathoadrenal response during hypoglycemia increases adrenaline secretion, induces arrhythmias, and increases the cardiac workload (56, 57). Thus, it is assumed that high GV leads to CVD through endothelial dysfunction.

## 3. Relationship between GV and Diabetic Complications in Clinical Practice

### *Long-term GV*

The relationship between long-term GV and diabetic microvascular and macrovascular complications in clinical practice is shown in Table 2. Variations in HbA1c and fasting plasma glucose levels are reported to be more associated with diabetic vascular complications than with HbA1c alone (28, 29). A meta-analysis reported that HbA1c variability is associated with diabetic microvascular and macrovascular complications and mortality in both type 1 diabetes mellitus (T1DM) and T2DM (77).

However, although long-term GV is correlated with the mean blood glucose and HbA1c, its relationship with short-term GV is unclear (78). Furthermore, because no studies have focused on the effects of long-term GV on ROS generation, further studies are needed.

### *Short-term GV*

The relationship between short-term GV and diabetic complications in clinical practice is shown in Table 3. In cross-sectional studies involving patients with T2DM, short-term GV indices, such as SD and CV, and the TIR, which are assessed by CGM, are associated with diabetic retinopathy (DR), diabetic kidney disease, and diabetic peripheral neuropathy (DPN) (38-41, 68, 69). In addition, we reported that albuminuria and DPN were associated with the worsening of the TIR in Japanese patients with T2DM (42). For diabetic macrovascular complications, cohort studies have reported that short-term GV and the TIR, which are assessed by SMBG and CGM, are associated with CVD and cardiovascular death (71, 72, 74).

In contrast, analyses of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications for T1DM have reported that GV indices, such as SD and MAGE, which are assessed by SMBG, were not associated with DR or DPN (79, 80). Although the difference between SMBG and CGM may have affected the results (10, 81), a large-scale, prospective, long-term study is needed to clarify the relationship between short-term GV and diabetic complications.

## 4. Treatment Strategies to Minimize GV

### *Type 2 diabetes*

For the treatment of patients with diabetes mellitus, setting therapeutic targets for each patient and managing blood glucose while avoiding excessive hyperglycemia, large glucose fluctuation, and hypoglycemia are important. Dietary and exercise therapies are useful for GV suppression (82, 83); however, drug therapy is also quite effective. Some studies on the effects of antidiabetic drugs on GV are

**Table 2. Association of Long-term Glycemic Variability Metrics and Diabetic Complications.**

| Subjects | N | Design | Main GV metrics | Main results | Ref |
|---|---|---|---|---|---|
| Microvascular complications | | | | | |
| T1DM | 1,441 | RCT | HbA1c-SD | HbA1c-SD contributed to the development of DR and DN. | 28 |
| T2DM | 821 | Prospective cohort | HbA1c-SD | HbA1c-SD was independently associated with the development of microalbuminuria. | 58 |
| T2DM | 8,260 | Prospective cohort | HbA1c-SD | HbA1c-SD affected (albuminuric) CKD. | 59 |
| T1DM | 2,019 | Retrospective cohort | HbA1c-CV | HbA1c-CV was associated with an increased cumulative incidence and risk of DR. | 60 |
| T1DM | 35,891 | Retrospective cohort | HbA1c-CV | HbA1c-CV was independently associated with DR. | 61 |
| T2DM | 32,481 | Retrospective cohort | FG-CV, HbA1c-CV | FG-CV and HbA1c-CV predicted development of end-stage renal disease. | 62 |
| T2DM | 4,231 | Retrospective cohort | HbA1c-SD | HbA1c-SD was associated with the development of DKD. | 63 |
| T2DM | 36,152 | Retrospective cohort | FG-SD | FG-CV was significant predictors of diabetic polyneuropathy. | 64 |
| Macrovascular complications | | | | | |
| T2DM | 4,399 | RCT | FG-SD, HbA1c-SD | HbA1c-SD and FG-SD were associated with combined macrovascular and microvascular events and macrovascular events. | 29 |
| Chinese without CVD | 53,607 | Prospective cohort | FG-CV | FG-CV increased the risk of CVD and all-cause mortality. | 65 |
| T2DM | 1,791 | RCT | FG-CV, ARV | FG-CV and FG-ARV were significantly associated with CVD. | 30 |
| T2DM | 30,932 | Retrospective cohort | FPG-CV | FPG-CV was associated with PAD. | 66 |
| T2DM | 13,111-19,883 | Retrospective cohort | HbA1c variability score | HbA1c variability was associated with increased risks of all-cause mortality, CV events, and diabetic microvascular complications. | 67 |
| Diabetes | 624,237 | Retrospective cohort | FPG-VIM | As the quartile of FPG-VIM increased, the risk of stroke, MI, and all-cause mortality serially increased. | 31 |
| T2DM | 9,483 | RCT | HbA1c-CV, VIM | HbA1c variability indices were significantly associated with total mortality. | 32 |

GV: glycemic variability, T1DM: type 1 diabetes mellitus, RCT: randomized controlled trial, SD: standard deviation, DR: diabetic retinopathy, DN: diabetic nephropathy, T2DM: type 2 diabetes mellitus, CKD: chronic kidney disease, CV: coefficient of variation, FG: fasting glucose, DKD: diabetic kidney disease, CVD: cardiovascular disease, ARV: average real variability, PAD: peripheral artery disease, VIM: variation independent of the mean, MI: myocardial infarction

shown in Table 4.

The Japanese Clinical Practice Guideline for Diabetes recommends patient-oriented use of antidiabetic drugs according to the condition of each patient (1). In Japan, dipeptidyl peptidase-4 inhibitors (DPP-4is) are frequently used (42). DPP-4is stimulate insulin secretion in a glucose-dependent manner and improve GV, but do not induce hypoglycemia when used as a single agent (97). In fact, DPP-4is improve GV without increasing the risk of hypoglycemia (84-87), and a cohort study has reported a reduction in CVD incidence (98). In addition, α-glucosidase inhibitors (α-GIs) can improve postprandial blood glucose levels and suppress CVD (99), and we have reported that the combination of DPP-4is and α-GIs can regulate the dynamics of glucagon-like peptide-1 (GLP-1) secretion dynamics and improve GV indices, such as SD and MAGE (100). In contrast, a meta-analysis investigating the association of DPP-4is, GLP-1 receptor agonists (GLP-1RAs), and sodium-glucose cotransporter-2 inhibitors (SGLT-2is) with CV events showed that DPP-4is were not associated with lower CVD mortality, whereas SGLT-2is and GLP-1RAs were associated with lower CVD mortality (101).

SGLT-2is not only improve glycemic control by inhibiting SGLT-2 in the proximal tubule and promoting urinary glucose excretion, but also have an inhibitory effect on weight loss (102). In comparison to placebo, SGLT-2is have been reported to improve SD and the TIR assessed using CGM without increasing the risk of hypoglycemia (88-90). In a randomized comparison of sitagliptin and dapagliflozin, GV indices, such as CV and MAGE, were significantly improved after the administration of sitagliptin, whereas dapagliflozin was effective in improving cardiometabolic risk factors, such as weight loss, serum insulin reduction, serum uric acid reduction, and increasing high-density lipoprotein-cholesterol (91). Randomized controlled trials involving patients with T2DM have reported that SGLT-2is inhibited CVD mortality, heart failure-related hospitalization, and albuminuria development (103-106). Interestingly, the use of SGLT-2is also reduced hospitalization for heart failure in patients without diabetes, suggesting that SGLT-2is themselves have cardioprotective effects (107, 108). Thus, GV improvement may not account for the cardioprotective effect of an-

**Table 3. Association of Short-term Glycemic Variability Metrics and Diabetic Complications.**

| Subjects | N | Design | Main GV metrics | Main results | Ref |
|---|---|---|---|---|---|
| Microvascular complications | | | | | |
| T2DM | 3,262 | Cross-sectional | CGM-TIR | CGM-TIR was associated with DR. | 38 |
| T2DM | 982 | Cross-sectional | CGM-MAGE | CGM-MAGE was a significant independent contributor to DPN. | 68 |
| T2DM | 2,927 | Cross-sectional | CGM-SD | CGM-SD was associated with DR. | 69 |
| T2DM | 866 | Cross-sectional | CGM-TIR | CGM-TIR was associated with albuminuria. | 39 |
| DM with DPN | 364 | Cross-sectional | CGM-TIR | CGM-TIR was associated with painful diabetic neuropathy. | 40 |
| T2DM | 999 | Cross-sectional | CGM-SD, TIR | CGM metrics were associated with the severity of DR or albuminuria. | 41 |
| T2DM | 281 | Cross-sectional | CGM-TIR | CGM-TIR was associated with albuminuria and DPN. | 42 |
| T1DM | 1,440 | RCT | SMBG-TIR | SMBG-TIR was associated with DR and albuminuria. | 70 |
| Macrovascular complications | | | | | |
| DM with stroke | 674 | Prospective cohort | SMBG-J-index | High GV was associated with 3-month cardiovascular composite outcome. | 71 |
| DM with ACS | 327 | Cohort study | SMBG-SD | High GV was an independent predictive factor for midterm MACE. | 72 |
| T2DM | 2,275 | Cross-sectional | CGM-TIR | CGM-TIR was associated with CIMT. | 73 |
| T2DM | 6,225 | Prospective cohort | CGM-TIR | Lower TIR was associated with all cause and CVD mortality. | 74 |
| T2DM | 445 | Cross-sectional | CGM-SD, MAGE, TIR | CGM-derived metrics were significantly associated with high arterial stiffness. | 75 |
| T2DM | 853 | Cross-sectional | CGM-CV, TIR | Higher CGM-CV and lower CGM-TIR were associated with higher cf-PWV. | 76 |

GV: glycemic variability, T2DM: type 2 diabetes mellitus, CGM: continuous glucose monitoring, TIR: time in range, DR: diabetic retinopathy, MAGE: mean amplitude of glycemic excursions, DPN: diabetic peripheral neuropathy, SD: standard deviation, RCT: randomized controlled trial, SMBG: self-monitoring of blood glucose, ACS: acute coronary syndrome, MACE: major adverse cardiovascular events, CIMT: carotid intima-media thickness, CVD: cardiovascular disease, CV: coefficient of variation, cf-PWV: carotid-femoral pulse wave velocity

**Table 4. Effects of Hyperglycemic Agents on Glucose Variability.**

| Drug | Comparator | Subjects | Main results | Ref |
|---|---|---|---|---|
| Teneligliptin | Placebo | T2DM | Compared with placebo, teneligliptin reduced TAR, CV, SD, and MAGE without increasing hypoglycemia. | 84 |
| Trelagliptin | Alogliptin | T2DM | Trelagliptin and alogliptin reduced SD and MAGE without inducing hypoglycemia. | 85 |
| Sitagliptin | Glimepiride | T2DM | MAGE decreased significantly in the sitagliptin group, but no significant difference was observed in the glimepiride group. | 86 |
| Vildagliptin | Gliclazide | T2DM | SG and MODD were significantly lower in the vildagliptin group than in the gliclazide group, but MAGE was not significantly different between the two groups. | 87 |
| Empagliflozin | Placebo | T2DM | Empagliflozin improved postprandial blood glucose levels and increased TIR without increasing TBR. | 88 |
| Dapagliflozin | Placebo | T2DM | Compared with placebo, dapagliflozin improved postprandial glucose, TIR, MAGE, and HBGI. | 89 |
| Canagliflozin | Placebo | T1DM | Compared with placebo, canagliflozin improved daily mean glucose and SD assessed by SMBG, and increased TIR assessed by CGM. | 90 |
| Dapagliflozin | Sitagliptin | T2DM | Sitalgliptin was superior to dapagliflozin in improving SD, MAGE and CONGA. | 91 |
| Degludec | Glargine U-100 | T2DM | HbA1c was similar in both groups, degludec lowered episodes of severe hypoglycemia. Degludec was noninferior to glargine U-100 in terms of the incidence of CVD events. | 92 |
| Degludec | Glargine U-300 | T1DM | SD for degludec was non-inferior to that for glargine U-300. TAR and TBR were shorter and longer, respectively, for degludec than glargine U-300. | 93 |
| Dulaglutide | Glargine U-100 | T2DM | In combination with lispro, dulaglutide improved the proportion of CGM glucose values within the near-normoglycaemia range versus glargine U-100 without increasing TBR. | 94 |
| Ultra-rapid lispro | Lispro | T1DM | Mealtime URLi improved postprandial glucose compared to mealtime lispro. Postmeal URLi resulted in similar postprandial glucose control to mealtime lispro. | 95 |
| Faster aspart | Aspart | T1DM | Faster aspart improved postprandial glucose and reduced TBR compared to aspart. | 96 |

TAR: time above range, CV: coefficient of variation, SD: standard deviation, MAGE: mean amplitude of glycemic excursions, SG: sensor glucose, MODD: mean of daily differences, TIR: time in range, TBR: time below range, HBGI: high blood glucose index, SMBG: self-monitoring of blood glucose, CGM: continuous glucose monitoring, T1DM: type 1 diabetes mellitus, CONGA: continuous overlapping net glycemic action, CVD: cardiovascular disease, URLi: ultra-rapid lispro

tidiabetic agents. Further studies are absolutely needed to investigate whether short-term GV improvement is directly associated with a reduced incidence of macrovascular complications.

As the duration of diabetes increases, the pancreatic β-cell function decreases and the proportion of patients on insulin increases (42). When starting insulin, it has been reported that starting with basal insulin was associated with less weight gain and hypoglycemia in comparison to starting with prandial bolus insulin or pre-mixed insulin (109). For basal insulin preparations, glargine U-300 and insulin degludec provide more stable basal insulin compensation than conventional basal insulin preparations, such as neutral protamine Hagedorn and glargine U-100 (110, 111). In fact, a meta-analysis has shown that glargine U-300 and insulin degludec reduced nocturnal hypoglycemia more than glargine U-100 (112-114).

GLP-1RAs improve GV by stimulating insulin secretion in a blood glucose-dependent manner and have a weight-loss effect by inhibiting gastric emptying and suppressing appetite (115). Oral GLP-1 RA, semaglutide, is also available now. In comparison to glargine U-100, dulaglutide increases the time in the normoglycemic range without increasing the TBR (91). Moreover, the combination of basal insulin and lixisenatide improved GV without increasing the risk of hypoglycemia (116). In addition, a meta-analysis has reported that the combination of basal insulin and GLP-1RAs was associated with a lower risk of hypoglycemia and improved glycemic control in comparison to multiple insulin injections (MDI) (117). GLP-1 reduces oxidative stress and inflammation and improves the vascular endothelial function (115, 118, 119). Furthermore, GLP-1RAs reduce the oxidative stress and vascular endothelial dysfunction induced by hyperglycemia and hypoglycemia, suggesting that GLP-1 RAs themselves have a vasoprotective effect (115, 120).

### *Type 1 diabetes*

MDI is the basic therapy in T1DM with reduced endogenous insulin secretion. In Japan, SGLT-2is can be used in combination with insulin therapy for T1DM. The administration of SGLT-2is in patients with T1DM has been reported to significantly improve the TIR and GV without increasing the TBR (121). Alternatively, the concomitant use of SGLT-2is in patients with T1DM may increase the risk of diabetic ketoacidosis (122), and careful consideration should be given to indicated cases.

For basal insulin, insulin degludec and glargine U-300 provide more stable basal insulin compensation and are associated with a lower risk of nocturnal hypoglycemia in comparison to glargine U-100 in T1DM (112, 113, 123-125). Insulin lispro, insulin aspart, and insulin glulisine are used as bolus insulin. In addition, insulin preparations, such as ultra-rapid lispro (URLi) and faster aspart, which are added to conventional insulin lispro and insulin aspart to accelerate the rate of subcutaneous insulin absorption, can be used. In comparison to insulin lispro, URLi improves postprandial blood glucose levels and increases the daytime TIR, while decreasing nighttime the TBR (95). Moreover, faster aspart improves postprandial blood glucose levels more than insulin aspart, while reducing the TBR (96). In addition, it has been reported that continuous subcutaneous insulin infusion (CSII) therapy improves glycemic control and QOL while avoiding hypoglycemia, in comparison to frequent injection therapy (126).

The use of real-time CGM and flash glucose monitoring (FGM) reduces hypoglycemia and improves GV (127-129). Regardless of the method of insulin administration (e.g., MDI or CSII), the use of real-time CGM improves the TIR without increasing the TBR more than SMBG (130). Therefore, CGM may be considered for GV suppression in both T 1DM and T2DM.

## Conclusions

High GV is not only associated with diabetic complications but also may lead to hypoglycemia and a decreased QOL (11-17). In T1DM, the use of newer ultra-rapid-acting insulin preparations, such as URLi and faster aspart, improves GV (95, 96). In T2DM, the use of GLP-1RAs or SGLT-2is improves GV without increasing the risk of hypoglycemia (88-90, 117). Furthermore, GLP-1RAs and SGLT-2is have cardiovascular protective effects beyond GV (107, 108, 115). In both T1DM and T2DM, the use of real-time CGM or FGM improves GV, while avoiding hypoglycemia (126-128).

Various nonclinical and clinical studies have shown that high GV increases the risk of hyperglycemia, excessive blood glucose variability, and hypoglycemia, and subsequently induces oxidative stress, inflammation, platelet activation, and vascular endothelial dysfunction, which are associated with diabetic complications (44-55). In fact, long-term GV is associated with diabetic macrovascular complications (28-31, 65-67). However, reports on the relationship between long-term and short-term GV and oxidative stress are insufficient. Furthermore, there is no clear evidence of the association between short-term GV and diabetic vascular complications. Long-term prospective studies are needed to clarify the role of GV in the development and progression of diabetic complications.

**The authors state that they have no Conflict of Interest (COI).**

### *References*

1. Araki E, Goto A, Kondo T, et al. Japanese clinical practice guideline for diabetes 2019. Diabetol Int **11**: 165-223, 2020.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med **329**: 977-986, 1993.
3. U.K. Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients

with type 2 diabetes (UKPDS 33). Lancet **352**: 837-853, 1998.
4. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med **358**: 2545-2559, 2008.
5. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med **358**: 2560-2572, 2008.
6. Duckworth W, Abraira C, Moritz T, et al. Intensive glucose control and complications in American veterans with type 2 diabetes. N Engl J Med **360**: 129-139, 2009.
7. Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care **32**: 187-192, 2009.
8. Svendsen PA, Lauritzen T, Søegaard U, et al. Glycosylated haemoglobin and steady-state mean blood glucose concentration in type 1 (insulin-dependent) diabetes. Diabetologia **23**: 403-405, 1982.
9. Nathan DM, Turgeon H, Regan S. Relationship between glycated haemoglobin levels and mean glucose levels over time. Diabetologia **50**: 2239-2244, 2007.
10. Kusunoki Y, Katsuno T, Nakae R, et al. Evaluation of blood glucose fluctuation in Japanese patients with type 1 diabetes mellitus by self-monitoring of blood glucose and continuous glucose monitoring. Diabetes Res Clin Pract **108**: 342-349, 2015.
11. Rodbard D. Interpretation of continuous glucose monitoring data: glycemic variability and quality of glycemic control. Diabetes Technol Ther **11** (Suppl 1): S55-S67, 2009.
12. Ceriello A. The post-prandial state and cardiovascular disease: relevance to diabetes mellitus. Diabetes Metab Res Rev **16**: 125-132, 2000.
13. Zhao Q, Zhou F, Zhang Y, Zhou X, Ying C. Fasting plasma glucose variability levels and risk of adverse outcomes among patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Res Clin Pract **148**: 23-31, 2019.
14. Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care **38**: 2354-2369, 2015.
15. Qu Y, Jacober SJ, Zhang Q, Wolka LL, DeVries JH. Rate of hypoglycemia in insulin-treated patients with type 2 diabetes can be predicted from glycemic variability data. Diabetes Technol Ther **14**: 1008-1012, 2012.
16. Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia **50**: 2553-2561, 2007.
17. Penckofer S, Quinn L, Byrn M, Ferrans C, Miller M, Strange P. Does glycemic variability impact mood and quality of life? Diabetes Technol Ther **14**: 303-310, 2012.
18. Monnier L, Colette C, Owens DR. The application of simple metrics in the assessment of glycaemic variability. Diabetes Metab **44**: 313-319, 2018.
19. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol **7**: 221-230, 2019.
20. Monnier L, Colette C, Wojtusciszyn A, et al. Toward defining the threshold between low and high glucose variability in diabetes. Diabetes Care **40**: 832-838, 2017.
21. Service FJ, Molnar GD, Rosevear JW, Ackerman E, Gatewood LC, Taylor WF. Mean amplitude of glycemic excursions, a measure of diabetic instability. Diabetes **19**: 644-655, 1970.
22. McDonnell CM, Donath SM, Vidmar SI, et al. A novel approach to continuous glucose analysis utilizing glycemic variation. Diabetes Technol Ther **7**: 253-263, 2005.
23. Kovatchev BP, Cox DJ, Gonder-Frederick LA, et al. Assessment of risk for severe hypoglycemia among adults with IDDM: validation of the low blood glucose index. Diabetes Care **21**: 1870-1875, 1998.
24. Kovatchev BP, Cox DJ, Gonder-Frederick LA, Clarke W. Symmetrization of the blood glucose measurement scale and its applications. Diabetes Care **20**: 1655-1658, 1997.
25. Kovatchev BP, Otto E, Cox D, et al. Evaluation of a new measure of blood glucose variability in diabetes. Diabetes Care **29**: 2433-2438, 2006.
26. Molnar GD, Taylor WF, Ho MM. Day-to-day variation of continuously monitored glycaemia: a further measure of diabetic instability. Diabetologia **8**: 342-348, 1972.
27. 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 **43**: 1593-1603, 2019.
28. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1 diabetes: data from the diabetes control and complications trial. Diabetes Care **31**: 2198-2202, 2008.
29. Hirakawa Y, Arima H, Zoungas S, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. Diabetes Care **37**: 2359-2365, 2014.
30. Zhou JJ, Schwenke DC, Bahn G, Reaven P; VADT Investigators. Glycemic variation and cardiovascular risk in the veterans affairs diabetes trial. Diabetes Care **41**: 2187-2194, 2018.
31. Lee DY, Han K, Park S, et al. Glucose variability and the risks of stroke, myocardial infarction, and all-cause mortality in individuals with diabetes: retrospective cohort study. Cardiovasc Diabetol **19**: 144, 2020.
32. Sheng CS, Tian J, Miao Y, et al. Prognostic significance of long-term HbA1c variability for all-cause mortality in the ACCORD trial. Diabetes Care **43**: 1185-1190, 2020.
33. Kovatchev B. Glycemic variability: risk factors, assessment, and control. J Diabetes Sci Technol **13**: 627-635, 2019.
34. Martinez M, Santamarina J, Pavesi A, Musso C, Umpierrez GE. Glycemic variability and cardiovascular disease in patients with type 2 diabetes. BMJ Open Diabetes Res Care **9**: e002032, 2021.
35. Wójcicki JM. "J"-index. A new proposition of the assessment of current glucose control in diabetic patients. Horm Metab Res **27**: 41-42, 1995.
36. Carlson AL, Mullen DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. Diabetes Technol Ther **19**: S4-S11, 2017.
37. Ohigashi M, Osugi K, Kusunoki Y, et al. Association of time in range with hemoglobin A1c, glycated albumin and 1,5-anhydro-d-glucitol. J Diabetes Investig **12**: 940-949, 2021.
38. 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 **41**: 2370-2376, 2018.
39. 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 **22**: 768-776, 2020.
40. Yang J, Yang X, Zhao D, Wang X, Wei W, Yuan H. Association of time in range, as assessed by continuous glucose monitoring, with painful diabetic polyneuropathy. J Diabetes Investig **12**: 828-836, 2021.
41. Wakasugi S, Mita T, Katakami N, et al. Associations between continuous glucose monitoring-derived metrics and diabetic retinopathy and albuminuria in patients with type 2 diabetes. BMJ Open Diabetes Res Care **9**: e001923, 2021.
42. Kuroda N, Kusunoki Y, Osugi K, et al. Relationships between time in range, glycemic variability including hypoglycemia and types of diabetes therapy in Japanese patients with type 2 diabetes

mellitus: Hyogo Diabetes Hypoglycemia Cognition Complications study. J Diabetes Investig **12**: 244-253, 2021.
**43.** Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes **54**: 1615-1625, 2005.
**44.** Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature **414**: 813-820, 2001.
**45.** Monnier L, Mas E, Ginet C, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA **295**: 1681-1687, 2006.
**46.** Quagliaro L, Piconi L, Assaloni R, Martinelli L, Motz E, Ceriello A. Intermittent high glucose enhances apoptosis related to oxidative stress in human umbilical vein endothelial cells: the role of protein kinase C and NAD(P)H-oxidase activation. Diabetes **52**: 2795-2804, 2003.
**47.** Piconi L, Quagliaro L, Assaloni R, et al. Constant and intermittent high glucose enhances endothelial cell apoptosis through mitochondrial superoxide overproduction. Diabetes Metab Res Rev **22**: 198-203, 2006.
**48.** Kilpatrick ES, Rigby AS, Goode K, Atkin SL. Relating mean blood glucose and glucose variability to the risk of multiple episodes of hypoglycaemia in type 1 diabetes. Diabetologia **50**: 2553-2561, 2007.
**49.** Rama Chandran S, Tay WL, Lye WK, et al. Beyond HbA1c: comparing glycemic variability and glycemic indices in predicting hypoglycemia in type 1 and type 2 diabetes. Diabetes Technol Ther **20**: 353-362, 2018.
**50.** Wang J, Alexanian A, Ying R, et al. Acute exposure to low glucose rapidly induces endothelial dysfunction and mitochondrial oxidative stress: role for AMP kinase. Arterioscler Thromb Vasc Biol **32**: 712-720, 2012.
**51.** Wright RJ, Newby DE, Stirling D, Ludlam CA, Macdonald IA, Frier BM. Effects of acute insulin-induced hypoglycemia on indices of inflammation: putative mechanism for aggravating vascular disease in diabetes. Diabetes Care **33**: 1591-1597, 2010.
**52.** Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. Diabetes **57**: 1349-1354, 2008.
**53.** Paneni F, Beckman JA, Creager MA, Cosentino F. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Eur Heart J **34**: 2436-2443, 2013.
**54.** Wang J, Alexanian A, Ying R, et al. Acute exposure to low glucose rapidly induces endothelial dysfunction and mitochondrial oxidative stress: role for AMP kinase. Arterioscler Thromb Vasc Biol **32**: 712-720, 2012.
**55.** Gogitidze Joy N, Hedrington MS, Briscoe VJ, Tate DB, Ertl AC, Davis SN. Effects of acute hypoglycemia on inflammatory and pro-atherothrombotic biomarkers in individuals with type 1 diabetes and healthy individuals. Diabetes Care **33**: 1529-1535, 2010.
**56.** Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care **33**: 1389-1394, 2010.
**57.** Sun B, Luo Z, Zhou J. Comprehensive elaboration of glycemic variability in diabetic macrovascular and microvascular complications. Cardiovasc Diabetol **20**: 9, 2021.
**58.** Hsu CC, Chang HY, Huang MC, et al. HbA1c variability is associated with microalbuminuria development in type 2 diabetes: a 7-year prospective cohort study. Diabetologia **55**: 3163-3172, 2012.
**59.** Penno G, Solini A, Bonora E, et al. HbA1c variability as an independent correlate of nephropathy, but not retinopathy, in patients with type 2 diabetes: the Renal Insufficiency And Cardiovascular Events (RIACE) Italian multicenter study. Diabetes Care **36**: 2301-2310, 2013.
**60.** Hietala K, Wadén J, Forsblom C, et al. HbA1c variability is associated with an increased risk of retinopathy requiring laser treatment in type 1 diabetes. Diabetologia **56**: 737-745, 2013.
**61.** Hermann JM, Hammes HP, Rami-Merhar B, et al. HbA1c variability as an independent risk factor for diabetic retinopathy in type 1 diabetes: a German/Austrian multicenter analysis on 35,891 patients. PLoS One **9**: e91137, 2014.
**62.** Yang YF, Li TC, Li CI, et al. Visit-to-visit glucose variability predicts the development of end-stage renal disease in type 2 diabetes: 10-year follow-up of Taiwan diabetes study. Medicine (Baltimore) **94**: e1804, 2015.
**63.** Ceriello A, De Cosmo S, Rossi MC, et al. Variability in HbA1c, blood pressure, lipid parameters and serum uric acid, and risk of development of chronic kidney disease in type 2 diabetes. Diabetes Obes Metab **19**: 1570-1578, 2017.
**64.** Yang CP, Li CI, Liu CS, et al. Variability of fasting plasma glucose increased risks of diabetic polyneuropathy in T2DM. Neurology **88**: 944-951, 2017.
**65.** Wang A, Liu X, Xu J, et al. Visit-to-visit variability of fasting plasma glucose and the risk of cardiovascular disease and all-cause mortality in the general population. J Am Heart Assoc **6**: e 006757, 2017.
**66.** Yang CP, Lin CC, Li CI, et al. Fasting plasma glucose variability and HbA1c are associated with peripheral artery disease risk in type 2 diabetes. Cardiovasc Diabetol **19**: 4, 2020.
**67.** Li S, Nemeth I, Donnelly L, Hapca S, Zhou K, Pearson ER. Visit-to-visit HbA1c variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes. Diabetes Care **43**: 426-432, 2020.
**68.** Hu YM, Zhao LH, Zhang XL, et al. Association of glycaemic variability evaluated by continuous glucose monitoring with diabetic peripheral neuropathy in type 2 diabetic patients. Endocrine **60**: 292-300, 2018.
**69.** Lu J, Ma X, Zhou L, et al. Glycemic variability assessed by continuous glucose monitoring and the risk of diabetic retinopathy in latent autoimmune diabetes of the adult and type 2 diabetes. J Diabetes Investig **10**: 753-759, 2019.
**70.** Beck RW, Bergenstal RM, Riddlesworth TD, et al. Validation of time in range as an outcome measure for diabetes clinical trials. Diabetes Care **42**: 400-405, 2019.
**71.** Yoon JE, Sunwoo JS, Kim JS, et al. Poststroke glycemic variability increased recurrent cardiovascular events in diabetic patients. J Diabetes Complications **31**: 390-394, 2017.
**72.** Gerbaud E, Darier R, Montaudon M, et al. Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. Diabetes Care **42**: 674-681, 2019.
**73.** 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 **22**: 72-78, 2020.
**74.** Lu J, Wang C, Shen Y, et al. Time in range in relation to all-cause and cardiovascular mortality in patients with type 2 diabetes: a prospective cohort study. Diabetes Care **44**: 549-555, 2021.
**75.** Wakasugi S, Mita T, Katakami N, et al. Associations between continuous glucose monitoring-derived metrics and arterial stiffness in Japanese patients with type 2 diabetes. Cardiovasc Diabetol **20**: 15, 2021.
**76.** Foreman YD, van Doorn WPTM, Schaper NC, et al. Greater daily glucose variability and lower time in range assessed with continuous glucose monitoring are associated with greater aortic stiffness: the Maastricht study. Diabetologia **64**: 1880-1892, 2021.
**77.** Gorst C, Kwok CS, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. Diabetes Care **38**: 2354-2369, 2015.
**78.** Battelino T, Dovč K. Glycemic variability: the danger of a physiologically stable metric. J Clin Endocrinol Metab **105**: e3815-e 3817, 2020.
**79.** Kilpatrick ES, Rigby AS, Atkin SL. Effect of glucose variability on the long-term risk of microvascular complications in type 1

diabetes. Diabetes Care **32**: 1901-1903, 2009.

**80.** Siegelaar SE, Kilpatrick ES, Rigby AS, Atkin SL, Hoekstra JB, Devries JH. Glucose variability does not contribute to the development of peripheral and autonomic neuropathy in type 1 diabetes: data from the DCCT. Diabetologia **52**: 2229-2232, 2009.

**81.** Šoupal J, Škrha J Jr, Fajmon M, et al. Glycemic variability is higher in type 1 diabetes patients with microvascular complications irrespective of glycemic control. Diabetes Technol Ther **16**: 198-203, 2014.

**82.** Karstoft K, Clark MA, Jakobsen I, et al. The effects of 2 weeks of interval vs continuous walking training on glycaemic control and whole-body oxidative stress in individuals with type 2 diabetes: a controlled, randomised, crossover trial. Diabetologia **60**: 508-517, 2017.

**83.** Shukla AP, Dickison M, Coughlin N, et al. The impact of food order on postprandial glycaemic excursions in prediabetes. Diabetes Obes Metab **21**: 377-381, 2019.

**84.** Bae JC, Kwak SH, Kim HJ, et al. Effects of teneligliptin on HbA1c levels, continuous glucose monitoring-derived time in range and glycemic variability in elderly patients with T2DM (TEDDY study). Diabetes Metab J. Forthcoming.

**85.** Nishimura R, Osonoi T, Koike Y, Miyata K, Shimasaki Y. A randomized pilot study of the effect of trelagliptin and alogliptin on glycemic variability in patients with type 2 diabetes. Adv Ther **36**: 3096-3109, 2019.

**86.** Kim HS, Shin JA, Lee SH, et al. A comparative study of the effects of a dipeptidyl peptidase-IV inhibitor and sulfonylurea on glucose variability in patients with type 2 diabetes with inadequate glycemic control on metformin. Diabetes Technol Ther **15**: 810-816, 2013.

**87.** Vianna AGD, Lacerda CS, Pechmann LM, Polesel MG, Marino EC, Faria-Neto JR. A randomized controlled trial to compare the effects of sulphonylurea gliclazide MR (modified release) and the DPP-4 inhibitor vildagliptin on glycemic variability and control measured by continuous glucose monitoring (CGM) in Brazilian women with type 2 diabetes. Diabetes Res Clin Pract **139**: 357-365, 2018.

**88.** Nishimura R, Tanaka Y, Koiwai K, et al. Effect of empagliflozin monotherapy on postprandial glucose and 24-hour glucose variability in Japanese patients with type 2 diabetes mellitus: a randomized, double-blind, placebo-controlled, 4-week study. Cardiovasc Diabetol **14**: 11, 2015.

**89.** Henry RR, Strange P, Zhou R, et al. Effects of dapagliflozin on 24-hour glycemic control in patients with type 2 diabetes: a randomized controlled trial. Diabetes Technol Ther **20**: 715-724, 2018.

**90.** Rodbard HW, Peters AL, Slee A, Cao A, Traina SB, Alba M. The effect of canagliflozin, a sodium glucose cotransporter 2 inhibitor, on glycemic end points assessed by continuous glucose monitoring and patient-reported outcomes among people with type 1 diabetes. Diabetes Care **40**: 171-180, 2017.

**91.** 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 **19**: 1, 2020.

**92.** Marso SP, McGuire DK, Zinman B, et al. Efficacy and safety of degludec versus glargine in type 2 diabetes. N Engl J Med **377**: 723-732, 2017.

**93.** Miura H, Sakaguchi K, Otowa-Suematsu N, et al. Effects of insulin degludec and insulin glargine U300 on glycaemic stability in individuals with type 1 diabetes: a multicentre, randomized controlled crossover study. Diabetes Obes Metab **22**: 2356-2363, 2020.

**94.** Jendle J, Testa MA, Martin S, Jiang H, Milicevic Z. Continuous glucose monitoring in patients with type 2 diabetes treated with glucagon-like peptide-1 receptor agonist dulaglutide in combination with prandial insulin lispro: an AWARD-4 substudy. Diabetes Obes Metab **18**: 999-1005, 2016.

**95.** Malecki MT, Cao D, Liu R, et al. Ultra-rapid lispro improves postprandial glucose control and time in range in type 1 diabetes compared to lispro: PRONTO-T1D continuous glucose monitoring substudy. Diabetes Technol Ther **22**: 853-860, 2020.

**96.** Bode BW, Johnson JA, Hyveled L, Tamer SC, Demissie M. Improved postprandial glycemic control with faster-acting insulin aspart in patients with type 1 diabetes using continuous subcutaneous insulin infusion. Diabetes Technol Ther **19**: 25-33, 2017.

**97.** Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet **368**: 1696-1705, 2006.

**98.** Yang TY, Liaw YP, Huang JY, et al. Association of sitagliptin with cardiovascular outcome in diabetic patients: a nationwide cohort study. Acta Diabetol **53**: 461-468, 2016.

**99.** Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trial Research Group. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. JAMA **290**: 486-494, 2003.

**100.** Kusunoki Y, Katsuno T, Myojin M, et al. Effect of additional administration of acarbose on blood glucose fluctuations and postprandial hyperglycemia in patients with type 2 diabetes mellitus under treatment with alogliptin. Endocr J **60**: 431-439, 2013.

**101.** Zheng SL, Alistair J, Aghar-Jaffar R, et al. Association between use of sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists, and dipeptidyl peptidase 4 inhibitors with all-cause mortality in patients with type 2 diabetes. JAMA **319**: 1580-1591, 2018.

**102.** Abdul-Ghani MA, Norton L, Defronzo RA. Role of sodium-glucose cotransporter 2 (SGLT 2) inhibitors in the treatment of type 2 diabetes. Endocr Rev **32**: 515-531, 2011.

**103.** Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med **373**: 2117-2128, 2015.

**104.** Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med **377**: 644-657, 2017.

**105.** Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med **380**: 347-357, 2019.

**106.** Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med **380**: 2295-2306, 2019.

**107.** McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med **381**: 1995-2008, 2019.

**108.** Anker SD, Butler J, Filippatos G, et al. Effect of empagliflozin on cardiovascular and renal outcomes in patients with heart failure by baseline diabetes status: results from the EMPEROR-reduced trial. Circulation **143**: 337-349, 2021.

**109.** Holman RR, Farmer AJ, Davies MJ, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med **361**: 1736-1747, 2009.

**110.** Becker RH, Dahmen R, Bergmann K, Lehmann A, Jax T, Heise T. New insulin glargine 300 units·mL-1 provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units·mL-1. Diabetes Care **38**: 637-643, 2015.

**111.** Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H. Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab **14**: 944-950, 2012.

**112.** Díez-Fernández A, Cavero-Redondo I, Moreno-Fernández J, et al. Effectiveness of insulin glargine U-300 versus insulin glargine U-100 on nocturnal hypoglycemia and glycemic control in type 1

and type 2 diabetes: a systematic review and meta-analysis. Acta Diabetol **56**: 355-364, 2019.

**113.** Ratner RE, Gough SC, Mathieu C, et al. Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase 3 trials. Diabetes Obes Metab **15**: 175-184, 2013.

**114.** Heller S, Mathieu C, Kapur R, Wolden ML, Zinman B. A meta-analysis of rate ratios for nocturnal confirmed hypoglycaemia with insulin degludec vs. insulin glargine using different definitions for hypoglycaemia. Diabet Med **33**: 478-487, 2016.

**115.** Anagnostis P, Athyros VG, Adamidou F, et al. Glucagon-like peptide-1-based therapies and cardiovascular disease: looking beyond glycaemic control. Diabetes Obes Metab **13**: 302-312, 2011.

**116.** Umpierrez GE, O'Neal D, DiGenio A, et al. Lixisenatide reduces glycaemic variability in insulin-treated patients with type 2 diabetes. Diabetes Obes Metab **19**: 1317-1321, 2017.

**117.** Eng C, Kramer CK, Zinman B, Retnakaran R. Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis. Lancet **384**: 2228-2234, 2014.

**118.** Oeseburg H, de Boer RA, Buikema H, et al. Glucagon-like peptide 1 prevents reactive oxygen species-induced endothelial cell senescence through the activation of protein kinase A. Arterioscler Thromb Vasc Biol **30**: 1407-1414, 2010.

**119.** Ceriello A, Novials A, Canivell S, et al. Simultaneous GLP-1 and insulin administration acutely enhances their vasodilatory, antiinflammatory, and antioxidant action in type 2 diabetes. Diabetes Care **37**: 1938-1943, 2014.

**120.** Ceriello A, Novials A, Ortega E, et al. Glucagon-like peptide 1 reduces endothelial dysfunction, inflammation, and oxidative stress induced by both hyperglycemia and hypoglycemia in type 1 diabetes. Diabetes Care **36**: 2346-2350, 2013.

**121.** Mathieu C, Dandona P, Phillip M, et al. Glucose variables in type 1 diabetes studies with dapagliflozin: pooled analysis of continuous glucose monitoring data from DEPICT-1 and -2. Diabetes Care **42**: 1081-1087, 2019.

**122.** Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Sodium-glucose co-transporter-2 inhibitors as add-on therapy to insulin for type 1 diabetes mellitus: systematic review and meta-analysis of randomized controlled trials. Diabetes Obes Metab **20**: 1755-1761, 2018.

**123.** Kusunoki Y, Katsuno T, Miyakoshi K, et al. Effects of switching from insulin glargine or detemir to insulin degludec in patients with type 1 diabetes mellitus. Diabetes Ther **4**: 461-472, 2013.

**124.** Danne T, Matsuhisa M, Sussebach C, et al. Lower risk of severe hypoglycaemia with insulin glargine 300 U/mL versus glargine 100 U/mL in participants with type 1 diabetes: a meta-analysis of 6-month phase 3 clinical trials. Diabetes Obes Metab **22**: 1880-1885, 2020.

**125.** Matsuhisa M, Koyama M, Cheng X, et al. New insulin glargine 300 U/ml versus glargine 100 U/ml in Japanese adults with type 1 diabetes using basal and mealtime insulin: glucose control and hypoglycaemia in a randomized controlled trial (EDITION JP 1). Diabetes Obes Metab **18**: 375-383, 2016.

**126.** Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J. Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. Cochrane Database Syst Rev **20**: CD005103, 2010.

**127.** Heinemann L, Freckmann G, Ehrmann D, et al. Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet **391**: 1367-1377, 2018.

**128.** Oskarsson P, Antuna R, Geelhoed-Duijvestijn P, Kröger J, Weitgasser R, Bolinder J. Impact of flash glucose monitoring on hypoglycaemia in adults with type 1 diabetes managed with multiple daily injection therapy: a pre-specified subgroup analysis of the IMPACT randomised controlled trial. Diabetologia **61**: 539-550, 2018.

**129.** Breton MD, Patek SD, Lv D, et al. Continuous glucose monitoring and insulin informed advisory system with automated titration and dosing of insulin reduces glucose variability in type 1 diabetes mellitus. Diabetes Technol Ther **20**: 531-540, 2018.

**130.** Šoupal J, Petruželková L, Grunberger G, et al. Glycemic outcomes in adults with T1D are impacted more by continuous glucose monitoring than by insulin delivery method: 3 years of follow-up from the COMISAIR study. Diabetes Care **43**: 37-43, 2020.