

Association of visit-to-visit glycemic variability with risk of cardiovascular diseases in high-risk Japanese patients with type 2 diabetes: A subanalysis of the EMPATHY trial

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Keywords

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ABSTRACT

Aims/Introduction: Long-term glycemic variability is important for predicting diabetic complications, but evaluation in a Japanese population is lacking. The aim of this study was to explore the relationship between visit-to-visit glycemic variability (VV) and cardiovascular diseases (CV) in Japanese patients with type 2 diabetes, using the prospective cohort of the EMPATHY trial.

Materials and Methods: Among 4532 participants with at least three HbA1c measurements, VV was defined using the coefficient of variation (CV-HbA1c). The outcomes were the composite cardiovascular endpoints, including cardiac, cerebral, renal, and vascular events. The odds ratios (ORs) for the development of outcomes were estimated by using logistic regression models.

Results: During a median follow-up of 38 months, 190 subjects developed CV events. The risk of developing CV events increased significantly with increasing quintile of CV-HbA1c, after multivariable adjustment including the mean-HbA1c (OR for the fifth vs first quintile, 1.73; 95%CI, 1.03–2.91; *P* for trend test = 0.003). There was a stronger association between CV-HbA1c and CV events in patients with a mean-HbA1c of <7% compared with those with a mean-HbA1c of ≥7% (OR per 1 standard deviation, 1.51; 95%CI, 1.23–1.85 and 1.13; 95%CI, 0.98–1.29, respectively; *P* for interaction = 0.02).

Conclusions: Increases of VV were associated with the risk of CV events in Japanese patients with type 2 diabetes independent of the mean-HbA1c. The long-term variability of HbA1c as well as the mean HbA1c might be an important glycemic indicator in the management of patients with type 2 diabetes, especially in those with a mean-HbA1c of <7%.

INTRODUCTION

Glycated hemoglobin (HbA1c), which reflects the mean glucose level over 1 to 2 months, is used to monitor glycemic control in patients with diabetes. Since lowering the HbA1c reduces the risk of diabetic complications^{1,2}, most of the current guidelines recommend a HbA1c of <7.0% for the management of patients with diabetes³.

Recently, a number of studies have reported adverse effects of visit-to-visit glycemic variability (VVV) over months to years in patients with type 2 diabetes independent of the mean HbA1c^{4–6}. Therefore, long-term glycemic variability assessed by HbA1c may be important for predicting future diabetic complications. However, the associations between VVV and cardiovascular diseases (CVs) have not been fully evaluated in a Japanese population.

The EMPATHY trial enrolled patients at hospitals and family practice clinics across Japan and used a multicenter,

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prospective, randomized, open-label, blinded endpoint (PROBE) design (clinical trial registration number: UMIN00003486)⁷⁻⁸. This study compared standard and intensive statin therapy in patients with diabetic retinopathy and hypercholesterolemia, as the primary prevention modality. In the present study, we aimed to characterize the relationship between VVV and CV events in Japanese patients with type 2 diabetes by using the prospective cohort of the EMPATHY trial.

MATERIALS AND METHODS

The study was carried out with the approval of the Keio University Institutional Review Board for Clinical Research (20190177) and conformed with Japanese ethical guidelines for clinical studies and the provisions of the Declaration of Helsinki. All participants provided written informed consent before enrollment by the investigators.

Study design

The details of the EMPATHY trial have been described previously⁷⁻⁹. In brief, 5042 patients with diabetic retinopathy and elevated LDL-cholesterol and without a history of coronary artery disease were randomly assigned in equal numbers to receive oral standard treatment with an LDL-cholesterol target of 100–120 mg/dL or intensive treatment with a target of <70 mg/dL. In the beginning of the trial, physical and laboratory evaluations and medical histories were obtained. During the treatment period, the laboratory data including HbA1c levels, body weight, and blood pressure were measured every 6 months. In the present study, we included the 4532 participants in the EMPATHY trial who had at least three HbA1c measurements; the mean number of HbA1c measurements was 6.7 ± 1.9 . The coefficient of variation was used as an index of VVV in HbA1c, which was defined as CV-HbA1c.

Outcomes

The outcomes in this study were defined based on the primary outcome of the EMPATHY study, which was described previously⁷⁻⁸. The outcome was the composite incidence of CV events, including cardiac, cerebral, renal, and vascular events. Renal events were defined as an at least two-fold increase in the serum creatinine level at baseline (>1.5 mg/dL) or the initiation of chronic dialysis, according to the original study^{7,8}.

Statistical analysis

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA). The level of significance was two-sided and set to 5% ($P < 0.05$). Data are presented as the mean \pm standard deviation for continuous variables or frequency and proportion for categorical data. The CV-HbA1c and mean-HbA1c levels were divided into quintiles. The linear trends in the characteristics of participants at baseline across the quintiles of CV-HbA1c and mean-HbA1c were assessed using a linear regression model for continuous outcomes and a logistic regression model for binomial outcomes.

The odds ratios (ORs) and 95% confidence intervals (CIs) per quintile of CV-HbA1c and mean-HbA1c for the development of outcomes were estimated by using logistic regression models. Model 1 consisted of sex and age as covariates, and smoking habits, duration of diabetes, body mass index (BMI), group of statin therapy, hypertension, diabetic nephropathy, diabetic neuropathy, estimated glomerular filtration rate (eGFR) at baseline, and the number of HbA1c measurements were added in Model 2. Model 3 included the factors in Model 2 and mean-HbA1c. The heterogeneity in the magnitude of the association between subgroups of each factor was assessed by adding multiplicative interaction terms of CV-HbA1c and mean-HbA1c with each subgroup in the relevant logistic model.

RESULTS

Participant characteristics

The baseline characteristics according to quintile of CV-HbA1c are shown in Table 1. Age, the number of HbA1c measurements, mean-HbA1c, baseline-HbA1c, plasma glucose, duration of diabetes, BMI, and diastolic blood pressure increased with increasing quintile of CV-HbA1c. The proportions of female subjects, smoking habits, diabetic nephropathy, and baseline-medication of insulin or sulfonylurea also increased with increasing quintile of CV-HbA1c.

Associations of CV-HbA1c with cardiovascular disease

This study had a median follow-up of 38 months; during this time, 190 subjects developed CV events. The cumulative incidence of CV events increased significantly with increasing levels of CV-HbA1c (P for linear trend test = 0.01) (Figure 1). This association remained unchanged after adjusting for factors of Model 1 or Model 2 (Table 2). The adjusted ORs in Model 2 for CV events were significantly higher in the fourth and fifth quintile of CV-HbA1c compared with that in the first quintile (adjusted OR: 2.15; 95%CI: 1.33–3.47; $P = 0.002$, adjusted OR: 1.98; 95%CI: 1.22–3.24; $P = 0.006$, respectively). This association was almost unchanged after additional adjustment for mean-HbA1c (Table 2).

Subgroup analyses were conducted to assess the difference in the association of CV-HbA1c with CV events between groups defined by age (<65, ≥ 65 years), sex (male, female), statin therapy (standard, intensive), BMI (<25, ≥ 25 kg/m²), eGFR (<60, ≥ 60 mL/min/1.73 m²), mean-HbA1c (<7, $\geq 7\%$), baseline-HbA1c (<7, $\geq 7\%$), and the absence or presence of other factors (Figure 2). There was no significant heterogeneity in the magnitude of the association between the subgroups of factors, except the subgroup of mean-HbA1c. When comparing the subgroups with mean-HbA1c, there was a stronger association between CV-HbA1c and CV events in patients with a mean-HbA1c of <7% (adjusted OR per 1 standard deviation, 1.51; 95%CI, 1.23–1.85 and 1.13; 95%CI, 0.98–1.29, respectively; P for interaction = 0.02).

As shown in Table S2, analyses were performed for each outcome. In total, 70 cardiac, 36 cerebral, 84 renal, and 10 vascular

Table 1 | Characteristics of subjects according to the quintile of CV-HbA1c

Characteristic	Quintile 1 (906)	Quintile 2 (907)	Quintile 3 (906)	Quintile 4 (907)	Quintile 5 (906)	<i>P</i> for trend
CV-HbA1c	0.59–3.95	3.95–5.56	5.56–7.32	7.32–10.07	10.07–45.42	
Male (%)	431 (47.6)	451 (49.7)	416 (45.9)	415 (45.8)	440 (48.6)	0.71
Age (years)	65.1 ± 9.5	64.5 ± 10.0	63.5 ± 10.0	61.9 ± 10.9	60.2 ± 11.5	<0.001
Number of HbA1c measurements	6.2 ± 1.9	6.7 ± 1.9	6.7 ± 1.9	6.9 ± 2.0	6.8 ± 2.0	<0.001
Mean HbA1c (%)	7.0 ± 0.8	7.3 ± 0.9	7.5 ± 0.9	7.7 ± 1.1	8.1 ± 1.2	<0.001
Baseline HbA1c (%)	6.9 ± 0.8	7.3 ± 1.0	7.5 ± 1.0	7.8 ± 1.2	8.3 ± 1.5	<0.001
Plasma glucose (mg/dL)	138 ± 43	148 ± 50	151 ± 49	162 ± 58	180 ± 72	<0.001
Duration of diabetes (years)	12.7 ± 9.2	13.5 ± 9.0	13.7 ± 8.9	12.9 ± 8.4	12.3 ± 8.2	0.11
Body mass index (kg/m ²)	24.9 ± 3.8	25.1 ± 4.0	25.5 ± 3.9	26.1 ± 4.5	26.8 ± 4.8	<0.001
Smoking habits (%)	140 (15.5)	166 (18.3)	157 (17.3)	168 (18.5)	203 (22.4)	<0.001
Family history (%)						
Diabetes	469 (51.8)	469 (51.7)	486 (53.6)	478 (52.7)	480 (53.0)	0.51
Coronary artery disease	113 (12.5)	126 (13.9)	125 (13.8)	102 (11.2)	114 (12.6)	0.49
Cerebrovascular disease	206 (22.7)	183 (20.2)	155 (17.1)	196 (21.6)	173 (19.1)	0.17
Intensive statin therapy (%)	427 (47.1)	465 (51.3)	461 (50.9)	432 (47.6)	460 (50.8)	0.49
LDL cholesterol (mg/dL)	106.1 ± 24.2	105.6 ± 24.9	105.5 ± 26.2	106.3 ± 27.8	106.7 ± 27.8	0.51
Hypertension (%)	639 (70.5)	632 (69.7)	656 (72.4)	672 (74.1)	621 (68.5)	0.93
Blood pressure (mmHg)						
Systolic	133.5 ± 16.9	134.4 ± 16.4	133.4 ± 16.5	134.5 ± 17.7	135.1 ± 18.2	0.07
Diastolic	73.3 ± 10.9	74.8 ± 10.8	74.2 ± 10.9	75.3 ± 11.9	76.6 ± 11.3	<0.001
Diabetic complications (%)						
Nephropathy	427 (47.1)	464 (51.2)	463 (51.1)	513 (56.6)	537 (58.9)	<0.001
Neuropathy	277 (30.1)	285 (31.4)	293 (32.3)	263 (29.0)	270 (29.8)	0.41
Estimated glomerular filtration rate (mL/min/1.73 m ²)	71.7 ± 18.7	72.5 ± 18.8	74.5 ± 19.3	75.7 ± 21.1	78.2 ± 22.1	<0.001
Baseline medications for type 2 diabetes (%)						
Insulin	249 (27.5)	295 (32.5)	334 (36.9)	327 (36.1)	319 (35.2)	0.01
Sulfonylurea	298 (32.9)	343 (37.8)	352 (38.9)	352 (38.9)	350 (38.6)	<0.001
Glinide	54 (6.0)	39 (4.2)	39 (4.3)	47 (5.2)	35 (3.9)	0.14
Alpha-glucosidase inhibitor	227 (25.1)	203 (22.4)	211 (23.3)	212 (23.4)	203 (22.4)	0.33
Biguanide	361 (39.8)	369 (40.7)	395 (43.6)	420 (46.3)	375 (41.4)	0.09
Thiazolidinedione	156 (17.2)	173 (19.1)	151 (16.7)	177 (19.5)	167 (18.4)	0.48
DPP-4 inhibitors	370 (40.8)	327 (36.1)	363 (40.1)	313 (34.5)	362 (40.0)	0.52
GLP-1 receptor agonist	6 (0.7)	6 (0.7)	14 (1.5)	17 (1.8)	14 (1.5)	0.01
The presence of plasma glucose <70 mg/dL in visits for this trial (%)	37 (4.1)	45 (5.0)	69 (7.6)	51 (5.6)	49 (5.4)	0.17

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

events occurred during the follow-up period. The adjusted ORs in Model 2 for cardiac and renal events increased significantly with increasing levels of CV-HbA1c (*P* for trend = 0.007 and 0.01, respectively).

Associations of mean-HbA1c with cardiovascular disease

The baseline characteristics according to quintiles of mean-HbA1c are shown in Table S1. The crude OR for CV events was not increased with increasing levels of mean-HbA1c (Table 3). However, the associations became significant after adjusting for the factors in Model 1 or Model 2 (Table 3). The multivariable-adjusted OR in Model 2 for CV events was significantly higher in the fifth quintile of mean-HbA1c compared

with that in the first quintile (adjusted OR: 1.85; 95%CI: 1.14–3.00; *P* = 0.01). In the magnitude of the association between subgroups of factors, there was no significant heterogeneity except for the subgroup of eGFR (Figure S1). There was a stronger association between mean-HbA1c and CV events in patients with an eGFR of ≥60 mL/min/1.73 m² (*P* for interaction = 0.01). As shown in Table S3, the multivariable-adjusted OR in Model 2 for cerebral events increased significantly with increasing levels of mean-HbA1c (*P* for linear trend test = 0.003).

We also performed an analysis of the associations between the variability or mean of plasma glucose and CV events (Tables S4 and S5). The results showed that the adjusted ORs

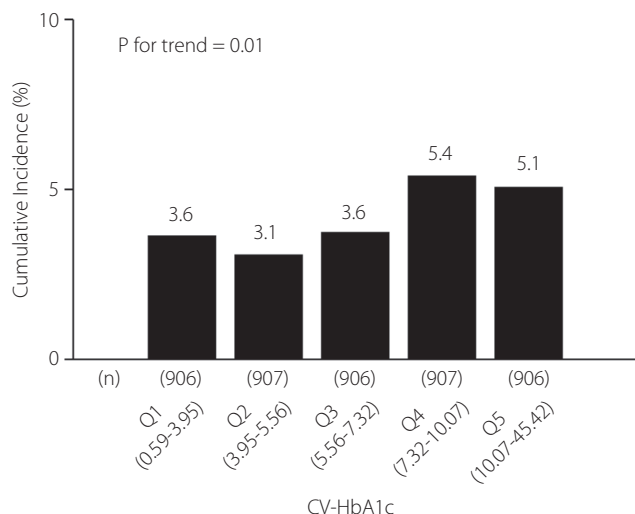


Figure 1 | The cumulative incidence of composite endpoints of cardiovascular disease according to the quintile of CV-HbA1c.

in Model 2 for CV events increased significantly with increasing levels of CV-plasma glucose and mean-plasma glucose (P for trend = 0.04 and 0.04, respectively).

DISCUSSION

The present study showed that elevated levels of CV-HbA1c were significantly associated with a greater risk of CV events in Japanese patients with type 2 diabetes, elevated LDL-cholesterol, and diabetic retinopathy beyond the factors included in mean-HbA1c. Intriguingly, this association was stronger in patients with a mean-HbA1c of <7%. Short-term glycemic variability has been shown to be associated with increased reactive oxygen species production and adverse outcomes^{10–12}. VVV was also reported to be associated with the risk for micro- and macrovascular complications and mortality in a systematic review and meta-analysis¹³, but the mechanisms underlying these associations remain unclear. Insulin resistance¹⁴, beta cell function⁴ or epigenetic changes^{15–16} may explain the association

of VVV and CV events. Our recent study showed that a time-in-range (TIR) of 70–180 mg/dL, as assessed by continuous glucose monitoring, was inversely correlated with CV-HbA1c¹⁷. Therefore, achieving a target TIR may be a practical strategy to improve CV-HbA1c. Considering the stronger influence of VVV and higher proportions of the presence of a plasma glucose of <70 mg/dL in visits for this trial with increasing quintile of CV-HbA1c (P for trend = 0.03, data not shown) in patients with a mean-HbA1c of <7%, the increased hypoglycemia in these subjects may also be related to the association of VVV and CV events. In fact, some studies reported that elevated levels of VVV were associated with episodes of or hospitalizations due to hypoglycemia^{18–19}. A previous study showed that there was a stronger association between VVV and CV events such as coronary artery disease, ischemic stroke, and progression to chronic kidney disease in patients with a mean HbA1c of <7%⁵, which is consistent with our results. These findings suggest that stable HbA1c control may prevent the incidence of CV events, especially in patients with a mean-HbA1c of <7%.

In this study, after adjusting for confounding factors, elevated levels of mean-HbA1c were also significantly associated with a greater risk of CV events in patients with type 2 diabetes. The fifth quintile of mean-HbA1c (8.2–13.6%) had the highest cumulative incidence of CV events, while the third quintile of mean-HbA1c (7.1–7.5%) had the lowest. A previous study reported that the risks of mortality and emergency hospitalization at a very low level of mean HbA1c (<6.09%) and at the highest level of mean HbA1c (>8.88%) were increased compared with the reference levels (6.09–6.58%)²⁰, and described a so-called J-shaped relationship. Furthermore, in the same study, the group with a mean HbA1c of 6.58–7.16% had the lowest incidence of emergency hospital admission for cardiovascular disease²⁰. Most guidelines recommend glycemic control of HbA1c to <7.0% to prevent diabetic complications³, particularly for microvascular outcomes². However, the benefits of a lower mean-HbA1c by tight glycemic control for CV events have been less clear²¹. Although lowering HbA1c reduces the risk of diabetic complications^{1,2}, intensive blood glucose normalization failed to reduce major cardiovascular events and conferred risks

Table 2 | The associations of CV-HbA1c with composite endpoints of cardiovascular disease

CV-HbA1c	No. of events/ subjects	Model 1			Model 2			Model 3		
		OR (95% CI)	P	P for trend	OR (95% CI)	P	P for trend	OR (95% CI)	P	P for trend
Quintile 1 (0.59–3.95)	33/906	1.00 (reference)	-	0.006	1.00 (reference)	-	<0.001	1.00 (reference)	-	0.003
Quintile 2 (3.95–5.56)	28/907	0.83 (0.50, 1.40)	0.48		0.99 (0.58, 1.70)	0.98		0.97 (0.57, 1.66)	0.91	
Quintile 3 (5.56–7.32)	34/906	1.07 (0.65, 1.74)	0.79		1.32 (0.79, 2.21)	0.29		1.26 (0.75, 2.12)	0.39	
Quintile 4 (7.32–10.07)	49/907	1.61 (1.02, 2.53)	0.04		2.15 (1.33, 3.47)	0.002		1.99 (1.22, 3.25)	0.006	
Quintile 5 (10.07–45.42)	46/906	1.50 (0.95, 2.39)	0.08		1.98 (1.22, 3.24)	0.006		1.73 (1.03, 2.91)	0.04	

OR, odds ratio; CI, confidence interval. Model 1: Adjustment was made for age and sex. Model 2: Adjustment was made for age, sex, body mass index, smoking habits, duration of diabetes, group of statin therapy, hypertension, diabetic nephropathy, diabetic neuropathy, estimated glomerular filtration rate and the number of HbA1c measurements. Model 3: Adjustment was made for the factors in Model 2 and mean-HbA1c.

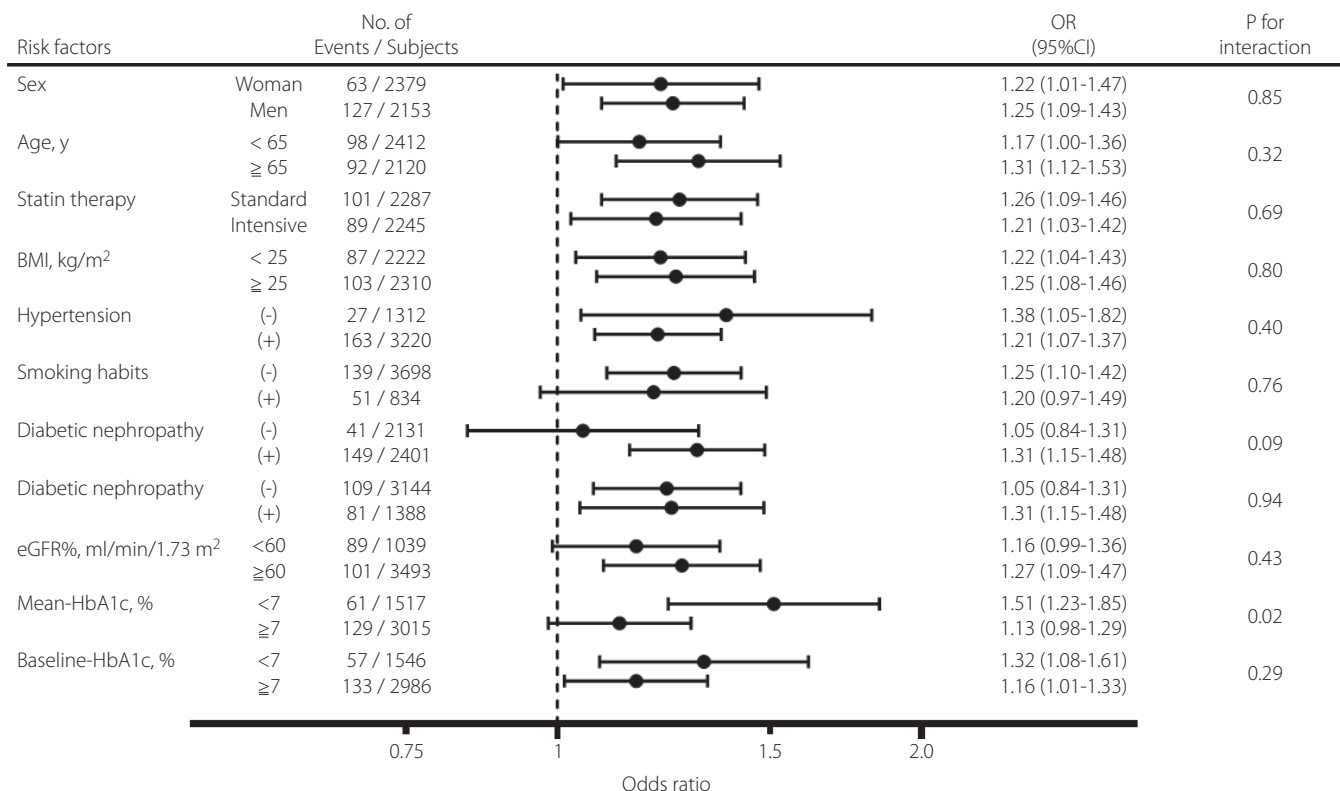


Figure 2 | Comparisons of the influence of CV-HbA1c on the development of composite endpoints of cardiovascular disease between subgroups. The values are shown as ORs and their 95% CIs per 1 standard deviation. The ORs were adjusted for age, sex, body mass index (BMI), smoking habits, duration of diabetes, group of statin therapy, hypertension, diabetic nephropathy, diabetic neuropathy, estimated glomerular filtration rate (eGFR), and the number of HbA1c measurements.

of increased mortality and hypoglycemia in the Action to Control Cardiovascular Risk in Diabetes trial²². In patients with type 2 diabetes, these findings suggest that poor glycemic control would increase the risk of CV events, but the advantages of achieving glycemic control of HbA1c to <7% in terms of avoiding CV events might be limited. Treatment avoiding glycemic variability and hypoglycemic events could be a better choice for type 2 diabetes patients with a mean-HbA1c of <7%. The use of insulin or sulfonylurea, which increases the risks of hypoglycemia, increased with a higher quintile of CV-HbA1c, and these drugs might have affected glycemic variability or CV events. Since it might be possible to normalize blood glucose and to avoid hypoglycemia by using incretin therapy or sodium-glucose cotransporter 2 inhibitors, further investigations including recent follow-up are needed.

This study had several limitations. First, the causality of the findings remains to be determined because the period of evaluation of HbA1c and the follow-up for endpoints were not distinguished. However, for each subject, we excluded all HbA1c data collected after the incidence of a CV event when evaluating CV-HbA1c or mean-HbA1c. Second, the statistical power for detecting the association between CV-HbA1c or mean-

HbA1c and each endpoint of CV events may have been limited by the small sample size and the short duration of follow-up for incidents. It may be necessary to interpret each complication, since, in this study, cerebral events were associated with mean-HbA1c, not CV-HbA1c. Third, this study enrolled type 2 diabetes patients with diabetic retinopathy and elevated LDL-cholesterol in Japan, and this population is at high risk for CV events. Thus, the results may not be applicable to those with a low risk for CV events, other ethnicities or type 1 diabetes. Fourth, measurement errors or differences in the methods used to measure HbA1c among centers might have affected the CV-HbA1c values, since multiple centers (hospitals and clinics) participated in this trial. However, there were no clear differences in the range or mean of CV-HbA1c compared with previous reports^{17,20}.

In conclusion, the current study showed that an increase of VVV was associated with an increased risk of CV events in Japanese patients with type 2 diabetes independent of mean HbA1c. The present findings suggest that the long-term variability of HbA1c as well as the mean HbA1c is an important glycemic indicator in the management of patients with type 2 diabetes, especially in those with a mean-HbA1c of <7%.

Table 3 | The associations of mean-HbA1c with composite endpoints of cardiovascular disease

Mean-HbA1c, %	No. of events/subjects				Model 1			Model 2		
		OR (95% CI)	P	P for trend	OR (95% CI)	P	P for trend	OR (95% CI)	P	P for trend
Quintile 1 (4.9–6.7)	38/907	1.00 (reference)	-	0.13	1.00 (reference)	-	0.04	1.00 (reference)	-	0.01
Quintile 2 (6.7–7.1)	33/901	0.87 (0.54, 1.40)	0.56		0.90 (0.56, 1.45)	0.67		1.10 (0.66, 1.81)	0.72	
Quintile 3 (7.1–7.5)	31/911	0.81 (0.50, 1.31)	0.38		0.85 (0.52, 1.37)	0.50		0.94 (0.56, 1.56)	0.80	
Quintile 4 (7.5–8.2)	38/907	1.00 (0.63, 1.58)	1.00		1.07 (0.67, 1.70)	0.77		1.28 (0.78, 2.10)	0.32	
Quintile 5 (8.2–13.6)	50/906	1.34 (0.87, 2.06)	0.19		1.54 (0.99, 2.34)	0.06		1.85 (1.14, 3.00)	0.01	

OR, odds ratio; CI, confidence interval. Model 1: Adjustment was made for age and sex. Model 2: Adjustment was made for age, sex, body mass index, smoking habits, duration of diabetes, group of statin therapy, hypertension, diabetic nephropathy, diabetic neuropathy, estimated glomerular filtration rate and the number of HbA1c measurements.

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DISCLOSURE

The study was carried out with the approval of the Keio University Institutional Review Board for Clinical Research on September 30, 2019 (Approval number: 20190177). M.S., J.I., and Y. Sato have no conflicts of interest to declare. Y. Saisho reports honoraria from Sumitomo Dainippon Pharma Co. I.K. reports honoraria from Astellas Pharma, AstraZeneca, MSD, Otsuka Pharmaceutical Co., Ono Pharmaceutical Co., Daiichi Sankyo Co., Takeda Pharmaceutical Co., Nippon Boehringer Ingelheim Co., Novartis Pharma K.K., Bayer Yakuhin, Pfizer Japan Inc., Bristol-Myers Squibb Co., and grants from Idorsia Pharmaceuticals Japan, Daiichi Sankyo Co., Takeda Pharmaceutical Co., Mitsubishi Tanabe Pharma Co. and Teijin Pharma. During the conduct of the study, H.I. reports grants and honoraria from Shionogi & Co. Outside the submitted work, H.I. reports grants and honoraria from Nippon Boehringer Ingelheim, MSD K.K., Daiichi Sankyo, Takeda Pharmaceutical, Mitsubishi Tanabe Pharma Corp., Taisho Toyama Pharmaceutical, and Shionogi & Co.; and grants from Astellas Pharma, Sumitomo Dainippon Pharma Co., Teijin Pharma, Kyowa Hakko Kirin, Mochida Pharmaceutical Co., Chugai Pharmaceutical, Ono Pharmaceutical Co., and Eli Lilly and Company, Japan K.K.; and personal fees from SBI Pharmaceuticals Co. and Nipro Corp.

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SUPPORTING INFORMATION

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

Figure S1 | Comparisons of the influence of mean-HbA1c on the development of composite endpoints of cardiovascular disease between subgroups. The values are shown as ORs and their 95% CIs per 1 standard deviation. The ORs were adjusted for age, sex, body mass index (BMI), smoking habits, duration of diabetes, group of statin therapy, hypertension, diabetic nephropathy, diabetic neuropathy, estimated glomerular filtration rate (eGFR), and the number of HbA1c measurements.

Table S1 | Characteristics of subjects according to the quintile of mean-HbA1c

Table S2 | The associations of CV-HbA1c with each endpoint of cardiovascular disease

Table S3 | The associations of mean-HbA1c with each endpoint of cardiovascular disease

Table S4 | The associations of CV-PG with composite endpoints of cardiovascular disease

Table S5 | The associations of mean-PG with composite endpoints of cardiovascular disease