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Prognostic impact of visit-to-visit glycemic variability on the risks of major adverse cardiovascular outcomes and hypoglycemia in patients with different glycemic control and type 2 diabetes

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Abstract

Purpose The prognostic impact of visit-to-visit glycemic variability on clinical outcomes in patients with different glycemic control and type 2 diabetes remains obscure. We investigated glucose variability and clinical outcomes for patients in the groups of Good glycemic control (GC), Insufficient glycemic control (IC), and Poor glycemic control (PC) in a prospective cohort study.

Methods By using data from Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation (ADVANCE), 930 patients were enrolled from 61 centers in China and grouped into GC, IC, and PC according to their glycated hemoglobin $A1_c$ ($HbA1_c$) and fasting plasma glucose (FPG). Visit-to-visit glycemic variability was defined using the coefficient of variation (CV) of five measurements of $HbA1_c$ and FPG taken 3–24 months after treatment. Multivariable Cox proportional hazards models were employed to estimate adjusted hazard ratio (aHR).

Results Among 930 patients in the intensive glucose control, 82, 538, and 310 patients were assigned to GC, IC, and PC, respectively. During the median of 4.8 years of follow-up, 322 patients were observed hypoglycemia and 244 patients experienced major adverse cardiovascular events (MACE). The CV of $HbA1_c$ and FPG was significantly lower for GC (6.0 ± 3.8, 11.2 ± 6.2) than IC (8.3 ± 5.6, 17.9 ± 10.6) and PC (9.5 ± 6.3, 19.3 ± 10.8). High glycemic variability was associated with a greater risk of MACE (aHR: 2.21; 95% confidence interval (CI): 1.61–3.03; $p < 0.001$) and hypoglycemia (aHR: 1.36; 95% CI: 1.04–1.79; $p = 0.025$) than low glycemic variability in total patients. The consistent trend was also found in subgroups of GC, IC, and PC.

Conclusions This prospective cohort study showed that glycemic variability was significantly lower for GC than IC and PC. Furthermore, glycemic variability was associated with the risk of MACE and hypoglycemia in total patients and subgroups of different glycemic control.

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Keywords Visit-to-visit glycemic variability · Different glycemic control · Type 2 diabetes · Major adverse cardiovascular events · Hypoglycemia

Abbreviations

GC	Good glycemic control
IC	Insufficient glycemic control
PC	Poor glycemic control
ADVANCE	Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation
$HbA1_c$	Glycated hemoglobin $A1_c$
FPG	Fasting plasma glucose
CV	Coefficient of variation
aHR	Adjusted hazard ratio
MACE	Major adverse cardiovascular events
SD	Standard deviations
BMI	Body mass index

Introduction

Diabetes is key contributor to mortality and morbidity worldwide, with a projected global prevalence of 629 million by 2045 [1]. Compared with people without diabetes, individuals with type 2 diabetes have a twofold higher risk of cardiovascular death and all-cause mortality [2]. Several studies demonstrated that intensive therapy effectively decreased the risk of microvascular complications [3, 4]. However, sequential analysis of randomized clinical trials reported a controversial association between intensive glucose control and cardiovascular diseases in patients with diabetes [5, 6]. Moreover, Bonds et al. [7] argued that intensive therapy was related to higher mortality, which might have, in part, been owing to hypoglycemia. In our previous study, we assigned the patients to groups of Good glycemic control (GC), Insufficient glycemic control (IC), and Poor glycemic control (PC), depending on the update mean value of both hemoglobin $A1_c$ ($HbA1_c$) and fasting plasma glucose (FPG), and explained, to some extent, no significant decrease in cardiovascular events with intensive glucose control [8]. Nevertheless, whether glycemic variability was associated with glycemic control and relative risk of major adverse cardiovascular events (MACE) and hypoglycemia remained obscure.

Glycemic variability is a physiological phenomenon that is a general denomination to several measures of short-term or long-term oscillations in glucose level. Short-term glycemic variability, characterized by within-day or between-day glycemic fluctuations, is generally measured by continuous glucose monitoring. Long-term glycemic variability, reflecting glycemic oscillations over months to years, is mainly measured by visit-to-visit variability in either HbA1c or FPG. Accumulating evidence indicated that glycemic variability increased the risk of not only cardiovascular diseases and mortality, but also hypoglycemia in diabetic patients [9–13]. Although our previous study evaluated the risk of MACE and hypoglycemia on the basis of levels of both $HbA1_c$ and FPG in GC, IC, and PC [8], little is known about the prognostic impact of visit-to-visit glycemic variability on MACE and hypoglycemia in type 2 diabetic patients with different glycemic control.

The aim of this study was to investigate the prognostic value of visit-to-visit glycemic variability for MACE as well as hypoglycemia in type 2 diabetic patients with different glycemic control.

Materials and methods

Study design and population

We conducted a prospective cohort study of patients from the linkable databases of ADVANCE, a factorial randomized and controlled trial at 61 centers in China. The study was approved by each center's institutional review board and was in accordance with the Declaration of Helsinki. All patients provided written informed consent (registration number NCT00145925). The follow-up schedule, design, and endpoints of the trial have been described in detail previously [14, 15].

Participants who were treated for 6 weeks as run-in period with fixed combination of perindopril and indapamide were randomly assigned (1:1) to receive modified release gliclazide-based intensive or standard therapy for glycemic control, and perindopril-indapamide or matching placebo for blood pressure control. The intensive glucose control received gliclazide-modified release-based regimen, other oral agents, and insulin to achieve for a $HbA1_c$ value of 6.5% or lower. The local standard therapy received usual glucose control regimens except the use of gliclazide. In our previous study, we have defined GC (target $HbA1_c$ <6.5% and FPG <6.1 mmol/L), IC (target $HbA1_c$ <6.5% and FPG ≥6.1 mmol/L, or $HbA1_c$ ≥6.5% and FPG <6.1 mmol/L), and PC (target HbA1c ≥ 6.5% and FPG ≥ 6.1 mmol/L) according to the recommendation for participant management in the intensive group by ADVANCE Collaborative Group [14].

In brief, we recruited a total of 1898 patients with type 2 diabetes aged 55 years or older who had a history of major macrovascular or microvascular disease, or at least one other risk factor for vascular disease. Further details of these patients had been described previously [16].

Primary analysis

Because of the unreliability to estimate glucose variability in the standard glucose treatment group, we only included 1005 patients in the intensive glucose treatment group in our primary analysis, in which a few measurements were taken ($HbA1_c$ was only measured at 6, 12, and 24 months during the follow-up, and FPG was first measured at 24 months). After exclusion of 61 ineligible patients during run-in period and 14 with missing values, 930 patients were included in the primary analysis.

Glycemic variability assessment

$HbA1_c$ and FPG was taken at baseline, at 3, 6, 12, 18, 24 months, and every 6 months thereafter in the intensive glycemic control. The intra-individual mean of $HbA1_c$ and FPG was calculated from the mean value of serially measured $HbA1_c$ and FPG in each participant. Visit-to-visit variability of $HbA1_c$ and FPG was evaluated using the five measurements at 3, 6, 12, 18, and 24 months, and measured as the standard deviation of $HbA1_c$ and FPG measurements. The coefficient of variation (CV) of $HbA1_c$ and FPG was used to correct for the mean. According to previous studies, we categorized the subjects into the groups of high glycemic variability and low glycemic variability on the basis of the median value of each $HbA1_c$ or FPG variability index [17, 18].

Follow-up and clinical outcomes

In our analyses of clinical outcomes, follow-up of patients lasted from their 24-month visit until they experienced events, deaths, or completed the final visit at the end of the study. MACE was identified as occurrence of any of an episode of major macrovascular events and major microvascular events. The major macrovascular events comprised of death from cardiovascular causes, non-fatal stroke, or non-fatal myocardial infarction. The microvascular events included new or worsening nephropathy or retinopathy. Hypoglycemia was recorded systematically as prespecified events of clinical interest and reviewed proactively with patients. All these adverse cardiovascular events were described and defined by previous studies [15], and adjudicated by an independent End Point Adjudication Committee without awareness of the group assignments.

Statistical analysis

Arithmetic means ± standard deviations (SD) were calculated for quantitative variables, while quantitative variables were given as frequency and percentage. Standardized differences in continuous variables during the follow-up period were analyzed with the use of linear mixed models. Multivariable Cox proportional hazards models were used to explore the association between risk factors and MACE or hypoglycemia. The inclusion of age, gender, body mass index (BMI), diabetes duration, baseline high- and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, baseline use of oral glucose-lowering agents, baseline use of insulin, mean hemoglobin $A1_c$ or fast plasma glucose during the first 24 months, history of major macrovascular diseases, history of major microvascular diseases, and smoking status as potential risk covariates was entered into the multivariable model. Freedom from occurrence of MACE was analyzed with Kaplan–Meier statistics, with difference between groups evaluated using the log-rank test. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

Results

Baseline clinical characteristics and glycemic variability

Baseline clinical characteristics of patients and visit-to-visit glycemic variability are summarized in Table 1. Complete case analyses were performed for 930 patients (75 ineligible patients were excluded) in the intensive glycemic control (Fig. 1). Mean age was 64.8 years, and 49.8% were male. According to the updated mean of $HbA1_c$ and FPG, 82 (8.8%), 538 (57.9%), and 310 (33.3%) patients were assigned to GC, IC, and PC, respectively. The SD and CV of $HbA1_c$ or FPG was significantly lower for GC than IC and PC. Correspondingly, the SD and CV of $HbA1_c$ for GC was 0.3 ± 0.2 and (6.0 ± 3.8)%, for IC was 0.6 ± 0.4 and (8.3 ± 5.6)%, and for PC was 0.8 ± 0.6 and (9.5 ± 6.3)%, respectively. Likewise, the SD and CV of FPG was also lower for GC than IC and PC. Accordingly, the SD and CV of FPG for GC was 0.6 ± 0.4 and (11.2 ± 6.2)%, for IC was 1.3 ± 0.9 and (17.9 ± 10.6)%, as well as for PC was 1.8 ± 1.2 and (19.3 ± 10.8)%, respectively. The median value of CV of $HbA1_c$ and FPG was 7.3% and 15.6%, respectively. Thus, patients with CV of $HbA1_c$ <7.3% or CV of FPG <15.6% was assigned to Low glycemic variability group, while those whose CV of $HbA1_c$ >7.3% or CV of FPG >15.6% belonged to High glycemic variability group.

Association between glycemic variability and MACE

During the follow-up period, 84 (34.4%) and 160 (65.6%) patients experienced MACE in Low glycemic variability group and High glycemic variability group. For the main analyses, Low glycemic variability group was selected as the reference regimen. Univariable regression analyses

Table 1 Baseline characteristics and visit-to-visit glycemic variability of patients in the intensive glucose control

Variables	Intensive glucose control group			*P* value
	Good glycemic control ($n = 82$)	Insufficient glycemic control ($n = 538$)	Poor glycemic control ($n = 310$)	
Demographics				
Age (years)	64.7 ± 5.3	64.9 ± 5.9	64.7 ± 6.1	0.813
Men (%)	54.9	50.0	48.1	0.542
Previous disease and medical history				
History of major macrovascular disease, *n* (%)	18.8	19.2	19.8	0.957
History of major microvascular disease, *n* (%)	6.1	7.2	8.5	0.730
Diabetes duration (years)	4.4 ± 5.2	7.7 ± 6.0	8.9 ± 6.2	<0.001
Current smokers, *n* (%)	22.5	24.6	23.8	0.744
Insulin (*n*%)	27.2	47.0	55.8	<0.001
Metformin (*n*%)	72.4	91.2	92.6	<0.001
CCBs (*n*%)	65.6	62.3	58.1	0.775
A-glucosidase inhibitors (*n*%)	44.5	61.2	61.3	0.535
Thiazolidinediones (*n*%)	15.4	18.9	16.8	0.678
Clinical parameters				
Baseline $HbA1_c$ (%)	6.6 ± 1.5	7.3 ± 1.4	8.8 ± 2.0	<0.0001
Baseline FPG (mmol/L)	6.6 ± 1.6	8.2 ± 2.5	10.3 ± 3.5	<0.0001
BMI (kg/m^2)	25.4 ± 3.2	25.4 ± 3.2	25.3 ± 3.2	0.904
SBP (mm Hg)	135.4 ± 20.6	138.6 ± 20.5	140.5 ± 22.2	0.126
DBP (mm Hg)	77.1 ± 10.0	77.9 ± 10.6	80.0 ± 12.1	0.014
TC (mmol/L)	5.3 ± 1.9	5.3 ± 1.2	5.5 ± 1.2	0.080
TG (mmol/L)	2.2 ± 4.1	1.9 ± 1.4	2.2 ± 1.5	0.048
HDL (mmol/L)	1.3 ± 0.4	1.3 ± 0.3	1.4 ± 0.4	0.002
LDL (mmol/L)	3.2 ± 5.2	3.0 ± 2.2	3.4 ± 1.0	0.057
$HbA1_c$ and FPG variability				
$HbA1_c$-mean (%)	5.8 ± 0.3	6.6 ± 0.7	7.7 ± 1.0	<0.0001
$HbA1_c$-SD (%)	0.3 ± 0.2	0.6 ± 0.4	0.8 ± 0.6	<0.0001
$HbA1_c$-CV (%)	6.0 ± 3.8	8.3 ± 5.6	9.5 ± 6.3	<0.0001
FPG-mean (%)	5.7 ± 0.6	7.1 ± 1.3	8.7 ± 1.8	<0.0001
FPG-SD (%)	0.6 ± 0.4	1.3 ± 0.9	1.8 ± 1.2	<0.0001
FPG-CV (%)	11.2 ± 6.2	17.9 ± 10.6	19.3 ± 10.8	<0.0001

Data are presented as mean ± SD or number (%) of subject

$HbA1_c$ glycated hemoglobin $A1_c$, *FPG* fasting plasma glucose, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TC* total cholesterol, *TG* triglyceride, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CCBs* calcium channel blockers, *$HbA1_c$-SD* standard deviation of $HbA1_c$, *$HbA1_c$-CV* coefficient of variation of $HbA1_c$, *FPG-SD* standard deviation of FPG, *FPG-CV* coefficient of variation of FPG

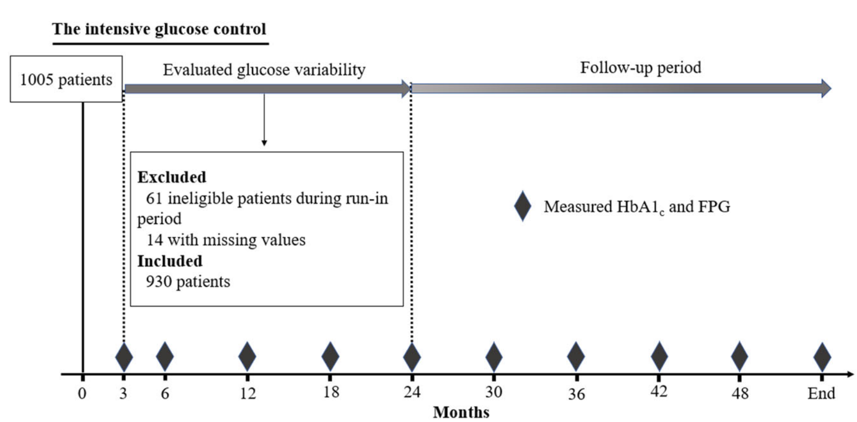

Fig. 1 Flowchart of the study protocol in the intensive glucose control

Table 2 Multiple adjusted Cox regression analyses for MACE

Group	MACE, *n* (%)[a]	Unadjusted HR	95% CI	*P* value	Adjusted HR[b]	95% CI	*P* value
Low glucose variability	84 (34.4)	1	Reference		1	Reference	
High glucose variability	160 (65.6)	2.35	1.74–3.19	<0.001	2.21	1.61–3.03	<0.001

MACE major adverse cardiovascular disease, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index

[a]MACE, major adverse cardiovascular disease, included combined macro- and microvascular events, primary macrovascular and microvascular events

[b]Adjusted for age, gender, BMI, diabetes duration, baseline high- and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, baseline use of oral glucose-lowering agents, baseline use of insulin, mean hemoglobin $A1_c$ or fast plasma glucose during the first 24 months, history of major macrovascular diseases, history of major microvascular diseases, and smoking status

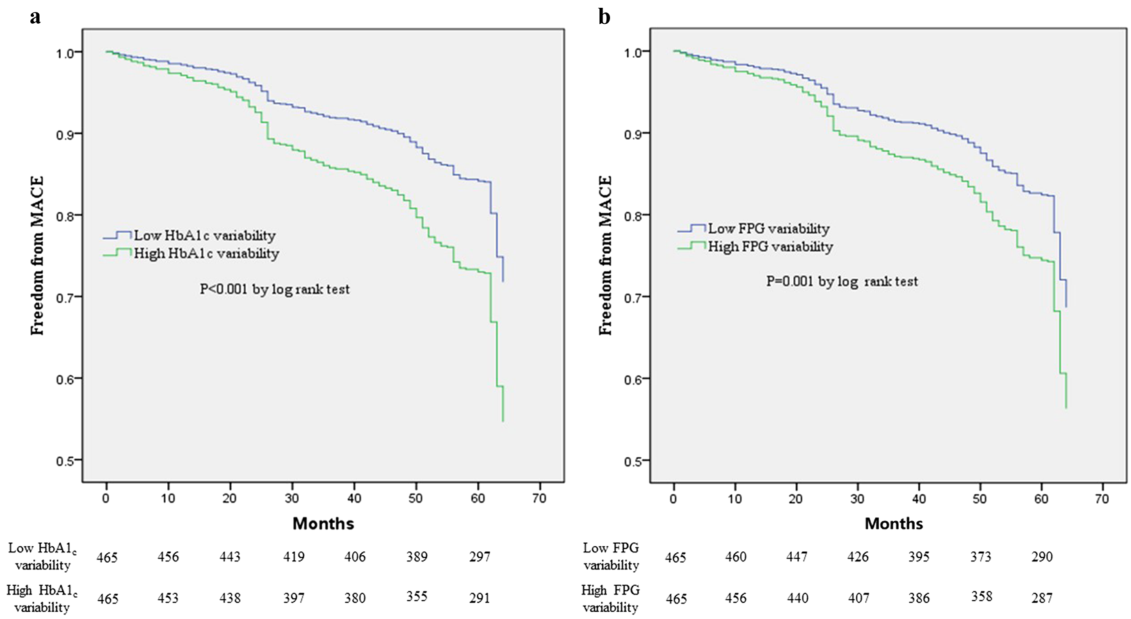

Fig. 2 Kaplan–Meier curves of freedom from major adverse cardiovascular disease (MACE) for glycemic variability in total patients. **a** Freedom from MACE for low and high glycated hemoglobin $A1_c$ ($HbA1_c$) variability. **b** Freedom from MACE for low and high fasting plasma glucose (FPG) variability. The numbers at the bottom of the figure are "number at risk"

showed that the absolute risk of MACE was significantly higher in High glycemic variability group (hazard ratio (HR): 2.35; 95% confidence interval (CI 1.74–3.19; $P < 0.001$) compared with Low glycemic variability group. We further performed the multiple regression analyses for MACE and found the consistent trend in High glycemic variability group (HR: 2.21; 95% CI: 1.61–3.03; $P < 0.001$) compared with Low glycemic variability group after adjusting for each of the following possible confounders including age, gender, BMI, diabetes duration, baseline high- and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, baseline use of oral glucose-lowering agents, baseline use of insulin, mean $HbA1_c$ or FPG during the first 24 months, history of major macrovascular diseases, history of major microvascular diseases, and smoking status (Table 2). The Kaplan–Meier plot for the occurrence of MACE between different glycemic variability levels was presented in Fig. 2.

Parallelly, we also explored the association between glycemic variability and MACE in subgroups of GC, IC, and PC. The percentage of subjects who experienced MACE was lower in those with low glycemic variability compared with high glycemic variability in subgroups of GC, IC, and PC (Supplementary Table 1).

Association between glycemic variability and hypoglycemia

The number of hypoglycemic episodes is provided in Table 3. During the follow-up period, 144 (44.7%) and 178 (55.3%) patients experienced hypoglycemic episodes in the Low glycemic variability group and High glycemic variability group. Univariable regression analyses revealed that the increased amplitude of glucose variability was associated with an elevated risk of hypoglycemia in the High glycemic variability group (HR: 1.42; 95% CI: 1.07–1.89;

Table 3 Multiple adjusted Cox regression analyses for hypoglycemic episodes

Group	Hypoglycemic episodes, *n* (%)	Unadjusted HR	95% CI	*P* value	Adjusted HR[a]	95% CI	*P* value
Low glucose variability	144 (44.7)	1	Reference		1	Reference	
High glucose variability	178 (55.3)	1.42	1.07–1.89	0.015	1.36	1.04–1.79	0.025

HR hazard ratio, *CI* confidence interval, *BMI* body mass index

[a]Adjusted for age, gender, BMI, diabetes duration, baseline high- and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, baseline use of oral glucose-lowering agents, baseline use of insulin, mean hemoglobin $A1_c$ or fast plasma glucose during the first 24 months, history of major macrovascular diseases, history of major microvascular diseases, and smoking status

$P = 0.015$) compared with the Low glycemic variability group. For multivariable regression analysis, variables, including age, gender, BMI, diabetes duration, baseline high- and low-density lipoprotein cholesterol, triglyceride, albumin-to-creatinine ratio, baseline use of oral glucose-lowering agents, baseline use of insulin, mean $HbA1_c$ or FPG during the first 24 months, history of major macrovascular diseases, history of major microvascular diseases, and smoking status, were entered into the multivariable Cox regression model. The result demonstrated that the risk of hypoglycemia was also associated with the High glycemic variability group (HR: 1.36; 95% CI: 1.04–1.79; $P = 0.025$) compared with the Low glycemic variability group.

Equally, we discovered that the percentage of individuals who experienced hypoglycemia was higher in high glycemic variability compared with low glycemic variability in subgroups of GC, IC, and PC (Supplementary Table 1).

Discussion

In our present study, we prospectively explored glycemic variability and clinical outcomes for T2DM patients with different glycemic control over a long-term follow-up period. Our current data demonstrated for the first time that the amplitude of glucose variability was lower for GC than IC and PC. We further discovered that higher glycemic variability was associated with an elevated risk of MACE and hypoglycemia compared with lower glycemic variability in total patients as well as subgroups of GC, IC, and PC, even after accounting for potential confounding factors. Our study suggested that increase in the visit-to-visit glycemic variability might have a detrimental impact on prognosis in T2DM patients with different glycemic control.

Previous epidemiologic researches argued that the relationship between glycemic control and cardiovascular outcomes had not been consistent [19–21]. Our recent study clarified a statistically significant increase in the risk of MACE in groups of IC or PC and explained, to some extent, no significant decrease in cardiovascular events with intensive glucose control [8]. Lately, Cardoso et al. [22] considered that visit-to-visit glycemic variability was a better parameter than HbA1c levels for assessing the risk of cardiovascular complications in T2DM patients. However, the relation between the amplitude of glycemic variability and the effect of glycemic control remained unknown. In the present analyses of study, glycemic variability was significantly lower for GC than IC and PC, which might be the leading cause for increased risk of cardiovascular complications in IC and PC. On the other hand, the different levels of glycemic variability in different glycemic control were also partially explained no significant decrease in cardiovascular events with intensive glucose control. Thus, glycemic control was considered critical to patients and clinicians against cardiovascular complications. With the increasing evidence supported that glycemic control should be individualized in T2DM patients [23–25], continuous glucose monitoring allowed clinicians to achieve a control of glycemic variability and optimize glycemic control.

Increasing literatures have indicated that glycemic variability was a potential predictor for diabetic complications and might play a key role in clinical risk assessment [26, 27]. However, a few studies suggested that HbA1c variability did not have a great effect on macrovascular complications in type 2 diabetes [28], and the effect of glycemic variability was even more controversial in type 1 diabetes [29]. Besides, the majority of existing literatures addressed the importance of glycemic variability from hour to hour, within a single day, or between days [12, 30, 31], but few studies have explored the impact of visit-to-visit glycemic variability on cardiovascular events, particularly in subgroups of different glycemic control. In the present study, glycemic variability was not only found to be associated with MACE and hypoglycemia in all patients, but also in subgroups after adjusting for clinical covariates, which signified that reducing the amplitude of glycemic variability was equally important for patients with good glycemic control.

Our study should be interpreted under the condition of several possible limitations. As a part of the ADVANCE trial with complex drug use, the possibility of residual confounding due to unmeasured or unknown risk factors cannot be ruled out. Furthermore, we are incapable of providing the accuracy of the particular assays used in each center to measure $HbA1_c$ and FPG. The major limitation of the present study might be the conventional antidiabetic drugs used during the treatment. Those different categories of antidiabetic agents have showed inconsistent beneficial effects on MACE and hypoglycemic episodes [14, 32, 33]. Moreover, researchers discovered that sulfonylurea was associated with the risk of hypoglycemia and glucose fluctuations, particularly in special populations [34, 35]. Nevertheless, Omori et al. [36] recommended that repaglinide reduced the glucose fluctuations in elderly patients with T2DM compared with sulfonylurea. Recently, a new class of oral antihyperglycemic agents, dipeptidyl peptidase-4 inhibitors reduced postprandial blood glucose levels and glucose fluctuations without increasing hypoglycemic risk [37], which were warranted for clinicians for selecting the optimal antihyperglycemic agents to avoid the high MACE rate in patients with T2DM.

It was widely recognized that certain mechanisms might be involved in the association between visit-to-visit glycemic variability and cardiovascular complications. Glucose fluctuation has been shown to cause an increase in inflammatory cytokines and overproduction of superoxide, which were involved in the progression of atherosclerosis [38, 39]. Our study did not measure the markers of superoxide and inflammatory cytokines, while further studies are needed to elucidate cause-and-effect relations and elaborated mechanism of glycemic variability and cardiovascular complications.

Conclusions

In conclusion, the amplitude of glucose variability was lower for patients with good glycemic control. Glycemic variability was associated with an elevated risk of MACE and hypoglycemia in patients with different glycemic control. These findings provided that future clinical strategies will not only target the effect of glycemic control, but also the amplitude of glucose variability.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the local ethics committee and was in accordance with the 1964 Declaration of Helsinki and its later amendmentsmed consent.

Informed consent All patients provide written informed consent.

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