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

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OBJECTIVE

There is no consensus on the importance of visit-to-visit glycemic variability in diabetes. Therefore, we assessed the effects of visit-to-visit variability (VVV) in HbA_{1c} and fasting glucose on major outcomes in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial.

RESEARCH DESIGN AND METHODS

ADVANCE was a factorial randomized controlled trial of intensive glucose control and blood pressure lowering in patients with type 2 diabetes. VVV in the intensive glucose treatment group was defined using the SD of five measurements of HbA_{1c} and glucose taken 3–24 months after randomization. Outcomes were combined macro- and microvascular events and all-cause mortality occurring post 24 months. Sensitivity analyses were performed using other indices of variability and in the standard glucose treatment group.

RESULTS

Among 4,399 patients in the intensive group, an increase in VVV of HbA_{1c} was associated with an increased risk of vascular events ($P = 0.01$) and with mortality ($P < 0.001$): highest versus lowest tenth hazard ratio (95% CI) 1.64 (1.05–2.55) and 3.31 (1.57–6.98), respectively, after multivariable adjustment. A clear association was also observed between VVV of fasting glucose and increased risk of vascular events ($P < 0.001$; 2.70 [1.65–4.42]). HbA_{1c} variability was positively associated with the risk of macrovascular events ($P = 0.02$ for trend), whereas glucose variability was associated with both macro- and microvascular events ($P = 0.005$ and $P < 0.001$ for trend, respectively). Sensitivity analyses using other indices, and patients in the standard glucose treatment group, were broadly consistent with these results.

CONCLUSIONS

Consistency of glycemic control is important to reduce the risks of vascular events and death in type 2 diabetes.

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Diabetes is an important cause of mortality and morbidity worldwide, through both direct clinical sequelae and increased mortality from cardiovascular and kidney diseases (1). Due to population aging and increasing obesity, diabetes is expected to rise globally from 152 million in 1980 to 552 million in 2030 (2,3). Effective prevention of diabetes-related premature death and morbidity requires better management and control of diabetes and other cardiovascular risk factors.

In the management of diabetes, underlying usual levels of HbA_{1c} and blood glucose (conceived as the true underlying average levels over a period of time) are widely considered to be of primary importance. Recently, a number of studies have raised concerns about possible adverse effects of visit-to-visit glycemic variability in diabetes (4–12). Therefore, glycemic variability has the potential to provide additional value in the prediction of future complications in diabetes. However, current evidence of the effect of visit-to-visit glycemic variability is insubstantial for macrovascular events in type 2 diabetes and is controversial in type 1 diabetes (13). There have also been several reports on the importance of variability from hour to hour, within a single day, or between days, which may reflect the influence of a variety of different mechanisms, but such short-term effects are not considered in this article (14–18).

The purpose of this study was to investigate the association of visit-to-visit variability (VVV) in HbA_{1c} and fasting glucose with the risks of microvascular events, macrovascular events, and all-cause mortality among patients with type 2 diabetes using data from the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial.

RESEARCH DESIGN AND METHODS

Study Design

ADVANCE was a factorial randomized controlled trial of blood pressure lowering and intensive blood glucose treatment in patients with type 2 diabetes. The design has been described in detail previously (19,20). In brief, a total of 11,140 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, were recruited from 215 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America between November 2001 and March 2003. Approval for the trial was obtained from each center's institutional review board, and all participants provided written informed consent.

Participants were randomly assigned to a fixed combination of perindopril and indapamide (2 mg/0.625 mg for the first 3 months and 4 mg/1.25 mg thereafter) or matching placebo, and to either an intensive glucose control strategy (target $HbA_{1c} \leq 6.5\%$) or a standard glucose control strategy based on local guidelines.

Primary Analysis

In our primary analysis, we only included patients in the intensive glucose treatment group because our study protocol made it unlikely that we could reliably estimate glucose variability in the standard glucose treatment group, in which few measurements were taken (HbA_{1c} was only measured at 6, 12, and 24 months during the first 2 years of follow-up, and glucose was first measured at 24 months). After excluding 452 patients who experienced study outcomes of macro- and microvascular events or death during the first 24 months and 720 with missing values of HbA_{1c} and/or fasting glucose (morning), 4,399 patients were included in the primary analysis (Fig. 1).

Glycemic Variability Assessment

Fasting samples for glucose assay and HbA_{1c} were taken at baseline, at 3, 6, 12, 18, and 24 months, and every 6 months thereafter in the intensive glucose treatment group. HbA_{1c} and fasting glucose were measured in local laboratories, and each HbA_{1c} measurement was standardized. Visit-to-visit variability (VVV) of HbA_{1c} or fasting glucose was evaluated using five measurements at 3, 6, 12, 18, and 24 months (Fig. 1). Measurements during the first 2 months were excluded in order to eliminate the effect of rapid reduction in HbA_{1c} in this early period. The SD, coefficient of variation (CV), variation independent of mean (VIM), residual standard deviation (RSD), and average real variability (ARV) were used as indices of VVV (21,22). Mean and maximum values of HbA_{1c} during the 24-month evaluation period were also used in the present analyses.

Follow-up and Study Outcomes

In all analyses of outcomes, follow-up of patients ranged from their 24-month visit until they experienced events, death, or they completed the final visit at the end of the study. The primary outcome was a composite of major macrovascular and major microvascular events. Secondary outcomes were major macrovascular events, major microvascular events, and all-cause mortality. Major macrovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Major microvascular events were defined as new or worsening nephropathy (development of macroalbuminuria, defined as a urinary albumin-creatinine ratio of >300 μg of albumin per milligram of creatinine, or doubling of serum creatinine level to at least 200 μmol/L, the need for renal

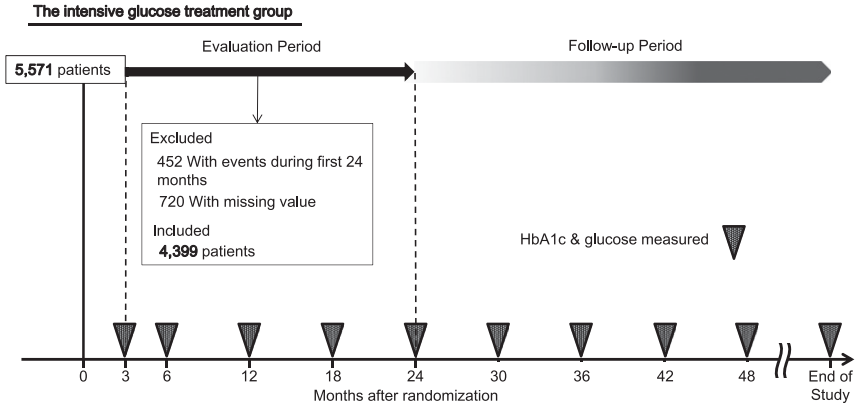

Figure 1—Flow diagram of the analysis in the intensive glucose treatment group.

replacement therapy, or death due to renal disease) or retinopathy (development of proliferative retinopathy, macular edema, or diabetes-related blindness or the use of retinal photocoagulation therapy).

Statistical Analysis

In order to test whether glycemic variability increased with time, the difference of the SD in glycemic variables between the first 2 years and thereafter was tested using a paired Student *t* test. Spearman correlation coefficients were estimated between measures of variability, maximum and mean HbA_{1c} or fasting glucose during the first 24 months. The effect of SD and maximum value of HbA_{1c} or fasting glucose were estimated by Cox proportional hazards models using groups defined by the deciles (the tenths). Adjustments were made for *1*) age, sex, and randomized blood pressure lowering; *2*) variables in model 1 plus region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, BMI, baseline use of oral glucose-lowering agents, and baseline use of insulin; and *3*) variables in model 2 plus mean of HbA_{1c} or fasting glucose during the first 24 months. A linear trend was tested using a quantitative ordinal variable ranging from 1 to 10 to represent the tenths. Hazard ratios (HRs) and 95% CIs for each tenth relative to lowest category and for each 10-percentile point increase (trend) in variability were estimated in each model. Effects of variability (SD, CV, VIM, RSD, and ARV), maximum value, and average of HbA_{1c} or fasting glucose as continuous variables were also investigated using Cox proportional hazards models, and HRs per one SD increments were reported.

Sensitivity analyses were performed *1*) using five measurements of HbA_{1c} or fasting glucose during 6–30 months to further eliminate the effect of early reduction in HbA_{1c} and *2*) using the models including the imputation of missing values of HbA_{1c} or fasting glucose among 720 patients using multiple imputation (23). The effects of SD of HbA_{1c} or fasting glucose were compared between subgroups defined by change in HbA_{1c} from 3 to 24 months within the range of −0.3 (−3.3) to 0.3% (3.3 mmol/mol) or larger. Sensitivity analyses in the standard glucose treatment group were also performed using three measurements at 6, 12, and 24 months (Supplementary Data). Finally, in order to assess the effect of randomized treatment, the SD of HbA_{1c} was evaluated from three measurements at 6, 12, and 24 months and compared between the intensive and standard glucose treatment groups. The heterogeneity between subgroups was tested by adding an interaction term. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). A two-sided $P < 0.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics and Glycemic Variability

Patient characteristics and visit-to-visit glycemic variability are summarized in Table 1. The patients in the intensive glucose treatment group excluded from the analysis included a group of 452 who experienced events in the first 24 months and was thus a high risk subset. However, the baseline characteristics of patients included in the analyses were similar to those for the total ADVANCE population. Mean age was 65.5 years, 42.6% were female, and 31.9% were recruited in Asia. Maximum of HbA_{1c} or fasting glucose was strongly correlated with mean HbA_{1c} or fasting glucose ($r > 0.90$ for maximum), whereas indicators of VVV had modest to little correlation with mean HbA_{1c} or fasting glucose during 3–24 months (r = 0.30–0.60 for SD, CV, RSD, and ARV; <0.15 for VIM) (Supplementary Table 1).

The mean SD of HbA_{1c} or fasting glucose for the intensive group was greater when estimated using five measurements rather than three (0.61 [6.7] vs. 0.56% [6.1 mmol/mol] for SD of HbA_{1c}; 1.41 vs. 1.32 mmol/L for SD of fasting glucose). The mean SD of HbA_{1c} or fasting glucose for the intensive group was significantly decreased from the first 2 years to the remaining follow-up period (SD of HbA_{1c} 0.60% [6.6 mmol/mol] during the first 2 years vs. 0.44% [4.8 mmol/mol] thereafter among 3,192 surviving patients, $P < 0.001$; SD of fasting glucose 1.38 mmol/L during the first 2 years vs. 1.16 mmol/L thereafter among 3,202 surviving patients, $P < 0.001$). The mean SD of HbA_{1c} derived from three measurements was slightly smaller in the intensive group than in the standard group (0.56 [6.1] vs. 0.61% [6.7 mmol/mol]).

Effect of VVV in HbA_{1c} or Fasting Glucose on Outcomes

Among 4,399 patients in the intensive glucose treatment group, there were 234 patients with major macrovascular events, 309 with major microvascular events, and 211 with deaths (43.1% for cardiovascular disease; 34.1% for cancer) during a median follow-up of 3.0 years (maximum 4.1 years) after completion of the 24-month visit. There were significant linear associations of SD of HbA_{1c} with combined macro- and microvascular events (P = 0.01 for trend), major macrovascular events (P = 0.02 for trend), and all-cause mortality ($P < 0.001$ for trend) even after adjusting for mean HbA_{1c} during the first 24 months and other confounding factors. SD of fasting glucose, adjusted for mean fasting glucose during the first 24 months and other factors, was also continuously associated with combined macro- and microvascular events ($P < 0.001$ for trend), major macrovascular events ($P < 0.001$ for trend), and major microvascular events (P = 0.005 for trend) (Fig. 2). These associations between SD of HbA_{1c} or fasting glucose and all outcomes were broadly similar for measurements during 6–30 months (Supplementary Fig. 1), and when missing values were imputed in the models (Supplementary Fig. 2). There was no heterogeneity in the effects of SD of HbA_{1c} or fasting glucose in subgroups defined by change in HbA_{1c} from 3 to 24 months within the range of −0.3 (−3.3) to 0.3% (3.3 mmol/mol) or larger (all P for heterogeneity >0.25 for any of four outcomes) (Supplementary Table 2). Similar results were obtained when different indicators of variability in HbA_{1c} or fasting glucose were used as continuous variables (Supplementary Tables 3 and 4).

There were no clear associations between maximum HbA_{1c} among five measurements and any of the four outcomes (Fig. 3). In contrast, maximum fasting glucose among five measurements had significant associations with combined macro- and microvascular events ($P < 0.001$ for trend), major macrovascular events (P = 0.01 for trend),

Table 1—Characteristics and visit-to-visit glycemic variability of patients included in the analysis of the intensive glucose treatment group and total patients in ADVANCE trial

	Intensive glucose treatment group		
Variables	Included patients (*n* = 4,399)	Excluded patients (*n* = 1,172)	Total ADVANCE (*n* = 11,140)
Demographics			
Age, years	65.5 ± 6.3	66.4 ± 6.6	65.8 ± 6.4
Men, %	42.6	42.7	42.5
Residence in East Asia*, %	31.9	20.5	29.6
Medical and lifestyle history			
History of major macrovascular disease, %	31.0	36.7	32.2
History of major microvascular disease, %	8.6	16.6	10.4
Baseline smoking status, %	15.4	15.7	15.1
Baseline alcohol intake, %	29.2	32.5	30.5
Duration of diabetes, %			
0–5 years	44.0	39.7	43.3
6–10 years	27.3	27.0	27.0
11–15 years	18.0	19.3	17.8
16+ years	10.7	14.0	11.9
Risk factors at baseline			
Systolic blood pressure, mmHg	144.4 ± 21.4	147.1 ± 22.6	145.0 ± 21.5
Diastolic blood pressure, mmHg	80.9 ± 11.0	80.4 ± 11.1	80.6 ± 10.9
Total cholesterol, mmol/L	5.2 ± 1.2	5.2 ± 1.2	5.2 ± 1.2
Triglyceride, mmol/L	1.6 (1.2–2.3)	1.6 (1.2–2.3)	1.6 (1.2–2.3)
BMI, kg/m^2	28.3 ± 5.1	28.5 ± 5.3	28.3 ± 5.2
Nonstudy blood pressure–lowering drug, %	74.7	76.5	75.1
Nonstudy glucose-lowering treatment			
Oral glucose-lowering agent, %	91.3	91.2	90.9
Insulin, %	1.5	1.5	1.4
Randomized intensive glucose lowering, %	100	100	50
Randomized perindopril-indapamide, %	50.1	49.3	50.0
HbA_{1c} or fasting glucose variability during the evaluation period using five measurements			
Mean HbA_{1c}, % (mmol/mol)	6.9 (52) ± 0.9 (9.8)	—	—
SD HbA_{1c}, % (mmol/mol)	0.6 (6.6) ± 0.4 (4.4)	—	—
Maximum HbA_{1c}, % (mmol/mol)	7.7 (61) ± 1.4 (15.3)	—	—
CV HbA_{1c}, %	8.6 ± 5.4	—	—
VIM HbA_{1c}, %	0.6 ± 0.3	—	—
RSD HbA_{1c}, % (mmol/mol)	0.5 (5.5) ± 0.4 (4.4)	—	—
ARV HbA_{1c}, % (mmol/mol)	0.6 (6.6) ± 0.5 (5.5)	—	—
Mean fasting glucose, mmol/L	7.6 ± 1.7	—	—
SD fasting glucose, mmol/L	1.4 ± 1.0	—	—
Maximum fasting glucose, mmol/L	9.4 ± 2.7	—	—
CV fasting glucose, mmol/L	17.9 ± 10.2	—	—
VIM fasting glucose, mmol/L	1.4 ± 0.7	—	—
RSD fasting glucose, mmol/L	1.3 ± 0.9	—	—
ARV fasting glucose, mmol/L	1.5 ± 1.4	—	—
HbA_{1c} or fasting glucose variability during the evaluation period using three measurements			
Mean HbA_{1c}, % (mmol/mol)	6.84 (51) ± 0.94 (10.3)	—	—
SD HbA_{1c}, % (mmol/mol)	0.56 (6.1) ± 0.47 (5.1)	—	—
Maximum HbA_{1c}, % (mmol/mol)	7.38 (57) ± 1.26 (13.8)	—	—
CV HbA_{1c}, %	7.87 ± 5.86	—	—
VIM HbA_{1c}, %	0.53 ± 0.37	—	—
RSD HbA_{1c}, % (mmol/mol)	0.44 (4.8) ± 0.49 (5.4)	—	—
ARV HbA_{1c}, % (mmol/mol)	0.67 (7.3) ± 0.60 (6.6)	—	—
Mean fasting glucose, mmol/L	7.51 ± 1.76	—	—
SD fasting glucose, mmol/L	1.32 ± 1.12	—	—
Maximum fasting glucose, mmol/L	8.81 ± 2.57	—	—
CV fasting glucose, mmol/L	16.9 ± 11.8	—	—
VIM fasting glucose, mmol/L	1.27 ± 0.85	—	—
RSD fasting glucose, mmol/L	1.11 ± 0.19	—	—
ARV fasting glucose, mmol/L	1.62 ± 1.47	—	—

Values are mean ± SD for continuous variables, median (interquartile range) for triglycerides, and percentage for categorical variables. HbA_{1c} values in IFCC-recommended units were reported in parentheses if appropriate. Higher value of each index of variability represents greater visit-to-visit glycemic variability. *Patients recruited in the Republic of China.

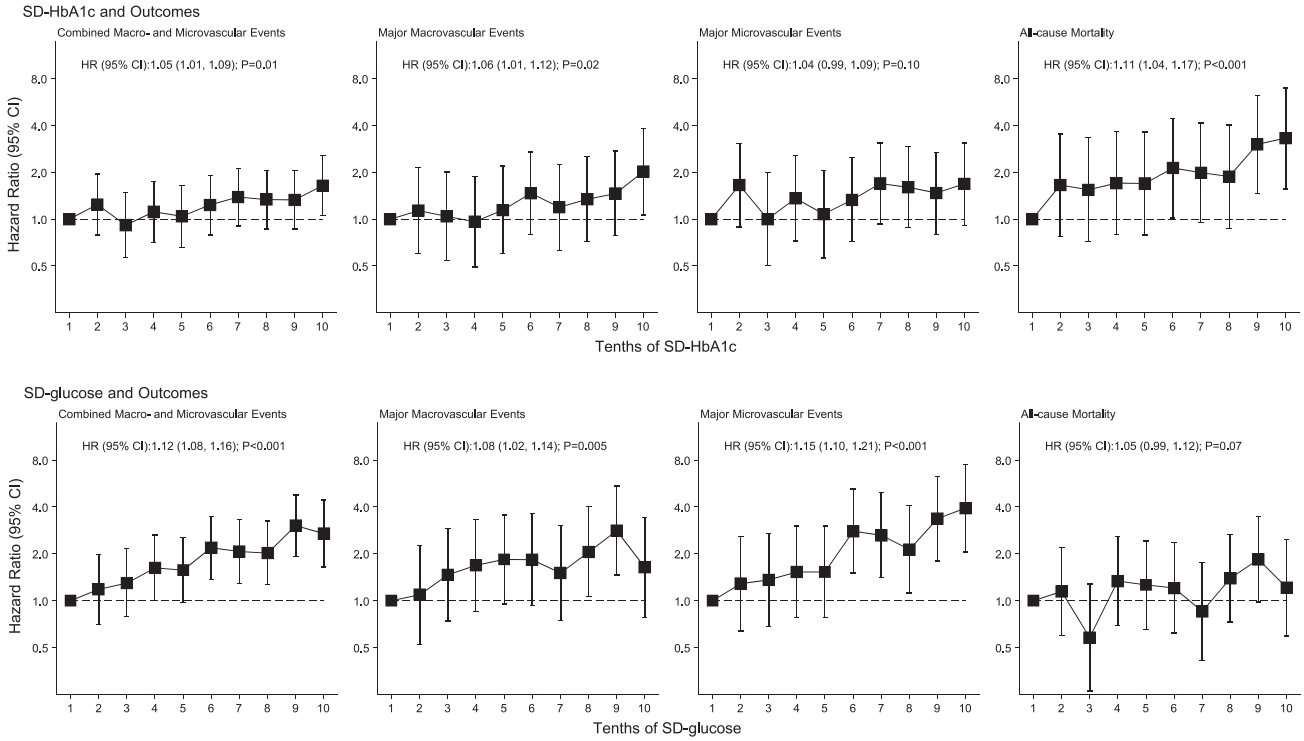

Figure 2—The effect of SD of HbA_{1c} or fasting glucose based on five measurements on the risks of outcomes in the intensive glucose treatment group. SD-HbA_{1c}, SD of HbA_{1c}; SD-glucose, SD of fasting glucose. HRs (95% CI) and *P* values were estimated for each 10-percentile point increase in SD of HbA_{1c} or fasting glucose. SD was estimated using five measurements at 3, 6, 12, 18, and 24 months after randomization. Adjustment was made for age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, BMI, baseline use of oral glucose-lowering agents, baseline use of insulin, and mean HbA_{1c} or fasting glucose during the first 24 months. The range of SD for each tenth group is $<$0.19 (2.1), 0.19 (2.1) to 0.26 (2.8), 0.27 (3.0) to 0.33 (3.6), 0.34 (3.7) to 0.40 (4.4), 0.41 (4.5) to 0.48 (5.2), 0.49 (5.4) to 0.58 (6.3), 0.59 (6.4) to 0.70 (7.7), 0.71 (7.8) to 0.88 (9.6), 0.89 (9.7) to 1.16 (12.7), and $\geq$1.17 (12.8), respectively, for HbA_{1c}, and $<$0.46, 0.46 to 0.63, 0.64 to 0.79, 0.80 to 0.96, 0.97 to 1.14, 1.15 to 1.34, 1.35 to 1.62, 1.63 to 2.00, 2.01 to 2.73, and $\geq$2.74, respectively, for fasting glucose.

and major microvascular events (*P* = 0.007 for trend) (Fig. 3). These associations between maximum HbA_{1c} or fasting glucose and all outcomes were broadly similar for measurements during 6–30 months (Supplementary Fig. 3) and when missing values were imputed in the models (Supplementary Fig. 4).

Sensitivity Analyses of Variability Based on Three Measurements in Standard Glucose Treatment Group

Sensitivity analyses were performed to elucidate the effect of VVV of HbA_{1c} in the standard glucose treatment group in which only three measurements of HbA_{1c} were available. For comparison, VVV of HbA_{1c} based on three measurements was also evaluated in the intensive glucose treatment group. There were no clear differences in the effects of SD of HbA_{1c} on any of four outcomes between the intensive and standard glucose treatment groups (all $P > 0.05$ for homogeneity) (Supplementary Fig. 5).

CONCLUSIONS

This is the first large-scale study to report the effects of VVV in both HbA_{1c} and fasting glucose on a variety of outcomes in type 2 diabetes, including macrovascular events. The present analyses revealed that VVV in HbA_{1c} as well as that in fasting glucose predicted future development of macrovascular events, microvascular events, and all-cause deaths independent of cardiovascular risk factors, including mean HbA_{1c} or fasting glucose, and study treatments. We have also shown that maximum value of fasting glucose was significantly associated with macrovascular and microvascular events. Both VVV and maximum of fasting glucose were stronger predictors than those of HbA_{1c} in that the HRs per decile increase were greater for both than those for HbA_{1c}.

Several medium-sized observational studies have reported positive associations between VVV in HbA_{1c} and development or progression of microalbuminuria in type 2 diabetes (8–10), but we are unaware of the results for other types of outcomes. In the present analyses of ADVANCE, the association between SD of HbA_{1c} and microvascular events did not reach statistical significance (*P* = 0.06 for trend) although this is the largest study of type 2 diabetes to date. Instead, there were clear associations of SD of HbA_{1c} with macrovascular events and all-cause mortality.

The outcomes studied in previous observational studies that assessed the effects of VVV in fasting glucose in patients with type 2 diabetes were retinopathy and mortality only (4–7,24). Most of those studies that investigated the risk of retinopathy reported positive associations (4,6,7). An Italian population-based prospective cohort study also demonstrated a positive association between VVV in fasting glucose and all-cause mortality (24). In the current study, VVV in fasting glucose during the first 2 years was significantly

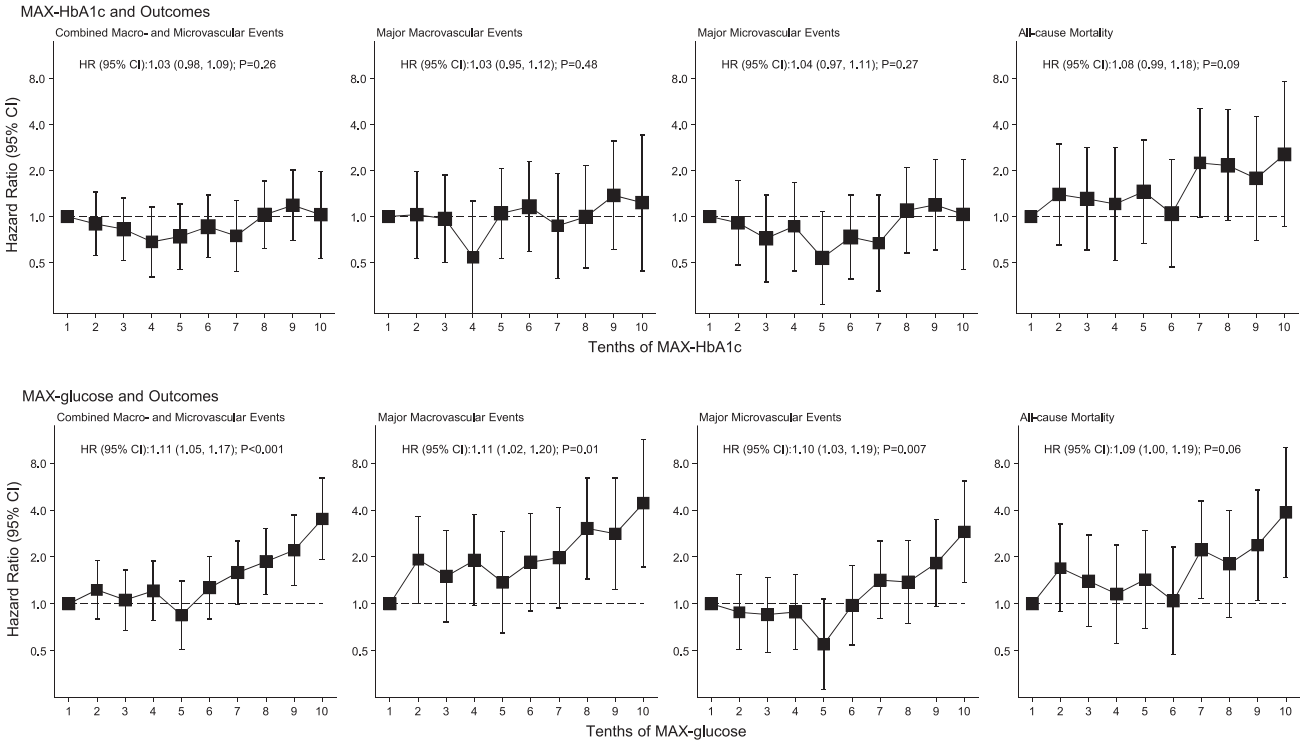

Figure 3—The effect of maximum of HbA_{1c} or fasting glucose among five measurements on the risks of outcomes in the intensive glucose treatment group. MAX-HbA_{1c}, maximum of HbA_{1c}; MAX-glucose, maximum of fasting glucose. HRs (95% CI) and *P* values were estimated for each 10-percentile point increase in maximum of HbA_{1c} or fasting glucose. Maximum value was the highest among five measurements at 3, 6, 12, 18, and 24 months after randomization. Adjustment was made for age, sex, randomized blood pressure lowering, region, duration of diabetes, baseline smoking status, baseline alcohol intake, systolic blood pressure, total cholesterol, log-transformed triglycerides, BMI, baseline use of oral glucose-lowering agents, baseline use of insulin, and mean HbA_{1c} or fasting glucose during the first 24 months. The range of maximum value for each tenth group is $<$6.3 (45), 6.3 (45) to 6.5 (48), 6.6 (49) to 6.7 (50), 6.8 (51) to 7.0 (53), 7.1 (54) to 7.3 (56), 7.4 (57) to 7.7 (61), 7.8 (62) to 8.0 (64), 8.1 (65) to 8.6 (70), 8.7 (72) to 9.5 (80), and $\geq$9.6 (81), respectively, for HbA_{1c}, and $<$6.5, 6.5 to 7.1, 7.2 to 7.7, 7.8 to 8.2, 8.3 to 8.8, 8.9 to 9.3, 9.4 to 10.1, 10.2 to 11.3, 11.4 to 13.0, and $\geq$13.1, respectively, for fasting glucose.

associated with elevated risk of microvascular events and marginally with increased mortality (*P* = 0.07 for trend). The present results confirmed the findings of the previous observational studies and expanded the current evidence to incident macrovascular events.

Several mechanisms may be involved in the association between visit-to-visit glycemic variability and outcomes. First, glucose fluctuation has been shown to cause overproduction of superoxide (25,26). The oxidative stress generation is a key factor of atherosclerosis (27,28). Second, glycemic fluctuation has also been shown to cause an increase in inflammatory cytokines and monocyte and macrophage adhesion to endothelial cells (28), which are involved in the progression of atherosclerosis. Third, transient hyperglycemia causes long-lasting epigenetic changes (29), which may promote systemic inflammation. Additionally, glucose fluctuation has also been shown to cause loss of pancreatic β-cells due to increased apoptotic cell death (30). The loss of pancreatic β-cells may result in deterioration of glycemic control (31) and subsequent progression of vascular complications or poor prognosis.

The strength of our study includes the large sample size and the rigorous evaluation of glycemic parameters and adjudication of major outcomes including macrovascular events. A limitation is possible selection bias due to exclusion of patients who experienced events during the first 24 months and those with missing values. However, baseline characteristics of patients included in the analyses were almost identical to those of the ADVANCE population (19), and the sensitivity analyses including imputation of missing values for visit-to-visit glycemic variability provided similar results. Second, SD may be overestimated among the patients who experienced continued improvement in blood glucose during the evaluation period from 3 to 24 months. However, sensitivity analyses using RSD, which is an indicator of variability completely independent of changes over time, showed comparable findings, suggesting that this limitation is not likely to invalidate the findings of the present analysis. Third, we are unable to provide the accuracy of the particular assays used in the individual centers to measure HbA_{1c} and fasting glucose. Fourth, the possibility of residual confounding by unmeasured or unknown risk factors remains. Fifth, since the current study is observational, clinical trials investigating the favorable effects of reducing glycemic variability are needed to elucidate any direct causality. Last, the effect of visit-to-visit glycemic variability could not be reliably explored in the standard glucose treatment group because measurements were few. However, broadly similar results were obtained in the sensitivity analyses using three measurements in both randomized groups.

In conclusion, VVV in HbA_{1c} and that in fasting glucose were associated with increased risks of macrovascular events,

microvascular events, and all-cause deaths in patients with type 2 diabetes. Intensive and consistent glucose control that achieves target HbA_{1c}/glucose levels recommended by current guidelines (32) with minimum fluctuation may provide further protection against future development of both macro- and microvascular complications and subsequent death in type 2 diabetes.

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