Prognostic Significance of Long-term HbA_{1c} Variability for All-Cause Mortality in the ACCORD Trial

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OBJECTIVE

The association between high glycemic variability and all-cause mortality has been widely investigated in epidemiological studies but rarely validated in glucose-lowering clinical trials. We aimed to identify the prognostic significance of visit-to-visit HbA_{1c} variability in treated patients in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial population.

RESEARCH DESIGN AND METHODS

We studied the risk of all-cause mortality in relation to long-term visit-to-visit HbA_{1c} variability, expressed as coefficient of variation (CV), variability independent of the mean (VIM), and average real variability (ARV), from the 8th month to the transition from intensive to standard glycemic therapy. Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratio (HR) and 95% CI.

RESULTS

Compared with the standard therapy group ($n = 4{,}728$), the intensive therapy group ($n = 4{,}755$) had significantly lower mean HbA_{1c} (6.6% [49 mmol/mol] vs. 7.7% [61 mmol/mol], $P < 0.0001$) and lower CV, VIM, and ARV ($P < 0.0001$). In multivariate adjusted analysis, all three HbA_{1c} variability indices were significantly associated with total mortality in all patients as well as in the standard- and intensive-therapy groups analyzed separately. The hazard ratios for a 1-SD increase in HbA_{1c} variability indices for all-cause mortality were 1.19 and 1.23 in intensive and standard therapy, respectively. Cross-tabulation analysis showed the third tertile of HbA_{1c} mean and VIM had significantly higher all-cause mortality (HR 2.05; 95% CI 1.17–3.61; $P < 0.01$) only in the intensive-therapy group.

CONCLUSIONS

Long-term visit-to-visit HbA_{1c} variability was a strong predictor of all-cause mortality. HbA_{1c} VIM combined with HbA_{1c} mean conferred an increased risk for all-cause mortality in the intensive-therapy group.

Type 2 diabetes is a common and potent risk factor for cardiovascular disease (CVD) events, and observational studies have consistently shown an association between the degree of hyperglycemia and the risk of these outcomes (1–4). However, several randomized clinical trials of intensive glycemic control in patients with type 2 diabetes did not demonstrate beneficial effects on these vascular outcomes (5–7). Moreover, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

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showed increased all-cause mortality in the intensive-treatment group compared with those receiving conventional treatment (8). In these clinical trials and in daily diabetes management in clinical practice, levels of glycated hemoglobin A_{1c} (HbA_{1c}) or blood glucose are considered of primary importance.

Recent observational studies in diabetes indicate that greater visit-to-visit glycemic variability is associated with macrovascular events as well as with microvascular complications (9–14). Two components of glycemic variability have been recognized: short-term, over days to weeks, and long-term glycemic variability. The latter may be ascertained by calculating visit-to-visit fluctuations of HbA_{1c} over periods of follow-up lasting months to years. An analysis of 58,832 patients with type 2 diabetes in primary care in the U.K. showed that HbA_{1c} variability was strongly associated with overall mortality and emergency hospitalization, and to a degree, this was not explained by average HbA_{1c} or hypoglycemic episodes (15). Furthermore, a post hoc analysis conducted in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) showed that greater visit-to-visit variability of fasting blood glucose was associated with increased mortality risk. However, the study just had three glucose measures and included patients with and without diabetes (16). Systematic ascertainment of glycemic variability may provide additional value in the prediction of future complications among patients with diabetes, both in clinical practice and in large clinical trials.

In the current study, we used data from the ACCORD trial to investigate associations of the long-term visit-to-visit variability in HbA_{1c} with outcomes among participants with type 2 diabetes and tested the hypothesis that HbA_{1c} variability might play an important role in outcomes of treated type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study Design

The ACCORD trial design, inclusion criteria, subject characteristics, and main results have been previously described (8,17–19) (online study protocols: https://biolincc.nhlbi.nih.gov/studies/accord/). In brief, the participants were between the ages of 40 and 79 years, had type 2 diabetes and an HbA_{1c} level of $\geq$7.5% (58.5 mmol/mol), had previous evidence of CVD or risk factors for CVD, and did not have a history of frequent or recent serious hypoglycemic events. The study randomly assigned 10,251 participants to receive comprehensive intensive glucose-lowering therapy targeting an HbA_{1c} level of $<$6.0% (42 mmol/mol) or standard therapy targeting a level of 7.0% (53 mmol/mol) to 7.9% (63 mmol/mol). HbA_{1c} levels were audited regularly according to treatment group and study center, and feedback was provided to facilitate attainment of the target HbA_{1c} levels. Patients in the intensive-therapy group attended monthly visits for the first 4 months and then every 2 months thereafter, with at least one interim telephone call, with the aim of rapidly and safely reducing HbA_{1c} levels to $<$6.0%. Patients in the standard-therapy group had glycemic management visits every 4 months. HbA_{1c} was measured every 4 months in the intensive-therapy and standard-therapy groups.

Compared with standard therapy, the use of intensive therapy to target normal HbA_{1c} levels for 3.5 years increased mortality and did not significantly reduce major cardiovascular events (8). The finding of higher mortality in the intensive-therapy group led to a decision to terminate the intensive regimen in February 2008. On 5 February 2008, participants were informed of the decision to discontinue the intensive glucose-lowering regimen after a mean treatment period of 3.7 years (17). Participants in the intensive-therapy group subsequently were switched to standard glycemic therapy. The "transition" variable in the ACCORD "activitystatus" data set specifies whether each visit for a subject was before or after the intensive glycemia intervention was stopped. In this study, the HbA_{1c} mean and variability were calculated using the data from the 8th month to the transition period, and the events of all-cause death were defined as those occurring before transition.

This report represents a post hoc analysis of data available for ACCORD participants in the intensive- and standard-therapy arms. To avoid the high glycemic variability brought about by the early-study stages of glucose lowering, we calculated the variability occurring after the 8th month of the study. After the patients whose HbA_{1c} was measured fewer than three times were excluded, 9,483 patients were included in the final analysis.

Statistics

For database management and statistical analysis, we used SAS 9.4 software (SAS Institute, Cary, NC). Significance was a two-tailed α level of $\leq$0.05. Means and proportions were compared using the large-sample z test and the χ^2 statistic, respectively.

Long-term visit-to-visit HbA_{1c} variability was evaluated using three or more HbA_{1c} measures from the 8th month to the transition, calculating individual participant coefficient of variation (CV), variation independent of the mean (VIM) (20), and average real variability (ARV) (21). CV was calculated as the SD divided by the mean, VIM as the SD divided by the mean to the power x and multiplied by the population mean to the power x, with x derived from curve fitting (20), and ARV as the average of the absolute differences between consecutive HbA_{1c} measurements. The association between HbA_{1c} variability and all-cause mortality was estimated by multivariable Cox proportional hazards models while adjusting for sex, therapy group, history of CVD, diabetes duration, mean of HbA_{1c} during visits, and age, education, waist circumference, BMI, systolic and diastolic blood pressure, triglycerides, and fasting plasma glucose at baseline.

HbA_{1c} variability was investigated as a continuous variable using Cox proportional hazards models, and the HRs of all-cause mortality for 1 SD increment in HbA_{1c} variability indices are reported. To allow for nonlinearity, a linear trend was tested using the variability indices in HbA_{1c} ranging from 1 to 10 to represent deciles. Hazard ratios (HRs) and 95% CIs for each decile relative to the first decile in the standard-therapy group and for each 10-percentile point increase in variability were estimated in a single model.

RESULTS

Characteristics of the Study Participants

Of all 10,251 participants, 9,483 had measurement of HbA_{1c} on at least three visits from the 8th month to the transition and were included in the final analysis. The baseline characteristics of patients included in the analyses were similar to those for the total ACCORD population. Mean age was 62.7 years, and 38.2% were women. Key baseline characteristics were similar in the two therapy groups (Table 1). Mean HbA_{1c} levels were relatively stable from the 8th month to the transition (Supplementary Table 1).

Table 1—Characteristics of the patients at baseline or during follow-up

		Therapy status		HbA_{1c} variability	
	All patients (N = 9,483)	Standard (n = 4,728)	Intensive (n = 4,755)	VIM <0.45 (n = 4,752)	VIM ≥0.45 (n = 4,731)
At baseline					
Age (years)	62.7 ± 6.6	62.8 ± 6.6	62.7 ± 6.6	63.0 ± 6.5	62.4 ± 6.6*
Female sex, n (%)	3,621 (38.2)	1,802 (38.1)	1,819 (38.3)	1,806 (38.0)	1,815 (38.4)
Weight (kg)	93.7 ± 18.4	93.7 ± 18.4	93.7 ± 18.4	92.2 ± 18	95.3 ± 18.6*
BMI (kg/m^2)	32.3 ± 5.4	32.3 ± 5.4	32.2 ± 5.4	31.8 ± 5.3	32.8 ± 5.4*
Waist circumference (cm)	106.8 ± 13.6	106.8 ± 13.5	106.8 ± 13.7	105.5 ± 13.3	108.1 ± 13.7*
Blood pressure					
Systolic (mmHg)	136.2 ± 16.9	136.4 ± 17.0	136.1 ± 16.8	135.6 ± 16.7	136.9 ± 17.2*
Diastolic (mmHg)	74.8 ± 10.6	74.9 ± 10.6	74.8 ± 10.6	74.3 ± 10.2	75.4 ± 10.9*
Fasting serum glucose (mg/dL)	175.2 ± 55.7	175.8 ± 55.9	174.7 ± 55.4	172.1 ± 53.1	178.4 ± 58.0*
Total cholesterol (mg/dL)	183.3 ± 41.8	183.4 ± 41.8	183.2 ± 41.8	182.2 ± 41.2	184.3 ± 42.3†
LDL cholesterol (mg/dL)	104.8 ± 33.7	104.9 ± 33.7	104.7 ± 33.7	104.5 ± 33.4	105.1 ± 34.1
Serum creatinine (mg/dL)	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.90 ± 0.22	0.92 ± 0.23*
During follow-up					
Mean HbA_{1c} (%)	7.1 ± 0.9	7.7 ± 0.7	6.6 ± 0.7*	7.1 ± 0.9	7.2 ± 0.9*
HbA_{1c} SD	0.5 ± 0.3	0.6 ± 0.4	0.4 ± 0.3*	0.3 ± 0.2	0.7 ± 0.4*
HbA_{1c} CV	0.08 ± 0.04	0.08 ± 0.04	0.06 ± 0.04*	0.04 ± 0.02	0.1 ± 0.04*
HbA_{1c} VIM	0.5 ± 0.2	0.51 ± 0.25	0.49 ± 0.2*	0.3 ± 0.1	0.7 ± 0.2*
HbA_{1c} ARV	0.5 ± 0.4	0.63 ± 0.39	0.39 ± 0.28*	0.3 ± 0.2	0.7 ± 0.4*

Continuous variables are shown as the means (SD) and categorical variables as indicated. HbA_{1c} of 7.1% converts to 54.1 mmol/mol, 7.7% to 61 mmol/mol, 6.6% to 49 mmol/mol, and 7.2% to 55.2 mmol/mol. *$P < 0.001$; †$P < 0.01$.

Compared with the standard-therapy group, the intensive-therapy group had significantly lower follow-up mean HbA_{1c} levels in the reduced subjects in our analysis (6.6% [49 mmol/mol] vs. 7.7% [61 mmol/mol], $P < 0.0001$) and significantly lower HbA_{1c} variability indices, including SD, CV, VIM, and ARV (all $P < 0.0001$) (Table 1). CV and ARV were more frequently distributed in higher deciles in the intensive-therapy group than in the standard-therapy group, but VIM was equally distributed in each decile (Supplementary Fig. 1).

Table 1 summarizes the characteristics of the participants by the median of the distribution of VIM. Compared with low HbA_{1c} variability (VIM <0.45 [the median value]), high HbA_{1c} variability (VIM ≥0.45) had a significantly lower baseline age; greater baseline body weight, baseline BMI, and waist circumference; and higher baseline systolic and diastolic blood pressure, fasting serum glucose, total cholesterol, and serum creatinine. High HbA_{1c} variability had a significantly higher mean HbA_{1c} level during follow-up and higher HbA_{1c} variability indices, including SD, CV, VIM, and ARV (Table 1).

Variability Indices and All-Cause Mortality

During the trial, all-cause mortality occurred in 168 and 190 subjects in the standard-therapy group and the intensive-therapy group, respectively. In multiple Cox regression analyses adjusted for sex, age, education, waist circumference, BMI, systolic and diastolic blood pressure, triglycerides, and fasting plasma glucose at baseline, all three HbA_{1c} variability indices were significantly ($P < 0.001$) associated with all-cause mortality. After further adjustment for the mean of HbA_{1c} during visits, all three HbA_{1c} variability indices were significantly ($P < 0.01$) associated with all-cause mortality. The hazard ratios for a 1-SD increase in HbA_{1c} variability indices for the all-cause mortality were 1.19–1.50 in the intensive-therapy group and 1.23–1.28 in the standard-therapy group. The ARV of HbA_{1c} showed greater HRs in the intensive therapy group (1.50 for a 1-SD increase) than in the standard-therapy group (1.28) (Table 2).

For all-cause mortality, the 10th decile of HbA_{1c} CV, VIM, and ARV had significantly higher risk in the intensive-therapy group but not in the standard-therapy group (Supplementary Fig. 1).

Cross-Tabulation Analysis of Mean and Variability

Since the HbA_{1c} CV and mean are correlated tightly (CV was calculated as the SD divided by the mean) and VIM was equally distributed in each decile in the intensive-therapy group and in the standard-therapy group, we used the VIM for cross-tabulation analysis. We conducted a cross-tabulation analysis of HbA_{1c} mean tertiles and VIM tertiles through the whole follow-up in relation to all-cause mortality (Table 3). Overall, as tertiles of HbA_{1c} mean and HbA_{1c} VIM increased, so did the incidence of all-cause mortality, and the third tertile of HbA_{1c} VIM combined with the third tertile of HbA_{1c} mean had the highest incidence of all-cause mortality (Fig. 1 and Supplementary Table 2).

Taking the first tertile of mean and VIM as reference, multiple Cox regression analyses were performed to calculate the HRs for other tertiles of mean and VIM. Importantly, for all-cause mortality, the third tertile of HbA_{1c} VIM had a significantly higher risk only in the third tertile of HbA_{1c} mean in the intensive-therapy group but not in the standard-therapy group (Table 3).

Percentage of Uncontrolled HbA_{1c} and All-Cause Mortality

Furthermore, we studied the HR for the risk of all-cause mortality in relation to the maximum and minimum HbA_{1c} and the percentage of uncontrolled HbA_{1c} during follow-up. In multiple Cox regression analyses, maximum and minimum HbA_{1c} were both associated with all-cause mortality in the intensive-therapy group.

Table 2—Association of mean and variability indexes of HbA_{1c} (from the 8th month to the transition) during follow-up with all-cause mortality

		Total population (n = 9,483)		Intensive therapy (n = 4,755)		Standard therapy (n = 4,728)	
Correlate (approximate + 1 SD)	Adjusted model	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
All-cause mortality							
Mean (+0.9%)	Model 1	1.26 (1.11–1.43)	0.0004	1.37 (1.16–1.61)	0.0002	1.13 (0.92–1.39)	0.23
CV (+0.04%)	Model 1	1.28 (1.16–1.40)	<0.0001	1.32 (1.16–1.51)	<0.0001	1.24 (1.08–1.42)	0.002
	Model 2	1.23 (1.11–1.36)	0.0001	1.22 (1.05–1.42)	0.01	1.23 (1.07–1.42)	0.005
VIM (+0.25 units)	Model 1	1.21 (1.10–1.33)	<0.0001	1.21 (1.06–1.37)	0.003	1.22 (1.06–1.40)	0.007
	Model 2	1.21 (1.10–1.33)	<0.0001	1.19 (1.04–1.35)	0.009	1.23 (1.07–1.42)	0.005
ARV (+0.36)	Model 1	1.37 (1.26–1.48)	<0.0001	1.50 (1.35–1.66)	<0.0001	1.26 (1.12–1.42)	0.0001
	Model 2	1.36 (1.23–1.50)	<0.0001	1.50 (1.30–1.75)	<0.0001	1.28 (1.12–1.46)	0.0004

Model 1 was adjusted for therapy group (if applicable), sex, history of CVD, diabetes duration, and baseline age, education, BMI, systolic and diastolic blood pressure, smoking, drinking, and fasting plasma glucose. Model 2 was adjusted for mean of HbA_{1c} during visits and the variables in model 1.

The HbA_{1c} of 7.0% (53 mmol/mol) and 8.0% (64 mmol/mol) were taken as the threshold for uncontrolled HbA_{1c} in the intensive-therapy and standard-therapy groups, respectively. Taking the percentage 0–19% as the reference, we found that increasing risks were shown with increased percentage of uncontrolled HbA_{1c} in general for all-cause mortality in the intensive-therapy group but not in the standard-therapy group. The HR for all-cause mortality with ≥80% uncontrolled HbA_{1c} in the intensive-therapy group was 1.67 (95% CI 1.11–2.52) (Supplementary Table 3).

CONCLUSIONS

In the current study, CV, VIM, and ARV in HbA_{1c} during visits were analyzed as indices of variability. The key findings can be summarized in two points: *1*) long-term visit-to-visit variability in HbA_{1c} was a powerful predictor of all-cause mortality, even when accounting for mean HbA_{1c}; and *2*) HbA_{1c} mean and HbA_{1c} variability were both risk factors for all-cause mortality, and higher HbA_{1c} variability combined with higher HbA_{1c} mean conferred an increased risk for all-cause mortality in the intensive-therapy group. These findings raised the issue that visit-to-visit glycemic variability as well as higher levels of glycemia might be important risk factors for all-cause mortality and should be considered in efforts to intensively lower glucose among individuals with type 2 diabetes.

Several previous observational studies in type 2 diabetes have shown HbA_{1c} variability is associated with micro- and macrovascular complications and mortality independently of the HbA_{1c} level. In a prospective cohort study conducted in 2,103 patients with diabetes in outpatient clinics (22), with an average follow-up of 6.6 years and a median of 10 HbA_{1c} measurements, HbA_{1c} CV significantly predicted diabetic nephropathy, defined as increased urinary albumin-to-creatinine ratio (HR 1.03 [95% CI 1.01–1.04] for 1% increase of CV). Lin et al. (23) performed a cohort study in 3,220 Chinese with diabetes living in Taiwan, with an average follow-up of 4.4 years and more than eight measurements of HbA_{1c}, and found that higher HbA_{1c} CV (>13.4%) was associated with greater risk of diabetic nephropathy, defined by an estimated glomerular filtration rate of <60 mL/min/1.73 m^2 (HR 1.58, 95% CI 1.19–2.11). Another study also performed in Taiwan in 881 patients with diabetes (24), with an average follow-up of 4.7 years and an average of 12 HbA_{1c} measurements, found that higher HbA_{1c} CV (>50th centile) was associated with greater risk of all-cause mortality (HR 1.06, 95% CI 1.01–1.11). Recently, a systematic review and meta-analysis showed that increased HbA_{1c} variability was associated with an increased risk of renal disease (risk ratio 1.34, 95% CI 1.08–2.25), cardiovascular events (risk ratio 1.27, 95% CI 1.15–1.40), and mortality (risk ratio 1.34, 95% CI 1.18–1.53) in type 2 diabetes (25).

Some studies also examined the HbA_{1c} variability in glucose-lowering clinical trials. There was a strong association between higher visit-to-visit glycemic variability and increased risk of mortality during the Veterans Affairs Diabetes Trial (VADT) that was independent of other traditional risk factors (26). Recent analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial showed that HbA_{1c} variability was positively associated with both total macrovascular events and major adverse cardiovascular events (27,28). That study

Table 3—Cross-tabulation of HbA_{1c} mean and variability tertiles in relation to all-cause mortality

	Intensive therapy			Standard therapy		
Tertiles	T1 of mean (≤6.22%)	T2 of mean (6.23–6.74%)	T3 of mean (>6.74%)	T1 of mean (≤7.35%)	T2 of mean (7.36–7.85%)	T3 of mean (>7.85%)
T1 of VIM (≤0.38 units)	—	0.74 (0.36–1.52)	1.18 (0.59–2.39)	—	0.72 (0.34–1.54)	0.99 (0.47–2.06)
T2 of VIM (0.39–0.57 units)	0.85 (0.44–1.66)	1.11 (0.59–2.10)	1.22 (0.64–2.33)	0.93 (0.46–1.86)	1.06 (0.53–2.10)	1.31 (0.65–2.65)
T3 of VIM (>0.57 units)	1.19 (0.63–2.25)	1.40 (0.76–2.60)	**2.05 (1.17–3.61)**	1.38 (0.72–2.66)	0.97 (0.47–2.03)	1.83 (0.94–3.55)

Data are presented as HR and 95% CI. All models were adjusted for mean of HbA_{1c} during visits, sex, history of CVD, diabetes duration, and baseline age, education, BMI, systolic and diastolic blood pressure, smoking, drinking, and fasting plasma glucose. T1, tertile 1; T2, tertile 2; T3, tertile 3. HbA_{1c} of 6.22% converts to 44.5 mmol/mol, 6.74% to 50.2 mmol/mol, 7.35% to 56.8 mmol/mol, and 7.85% to 62.3 mmol/mol. The third tertile of HbA_{1c} VIM had a significantly higher risk only in the third tertile of HbA_{1c} mean in the intensive-therapy group (boldface value).

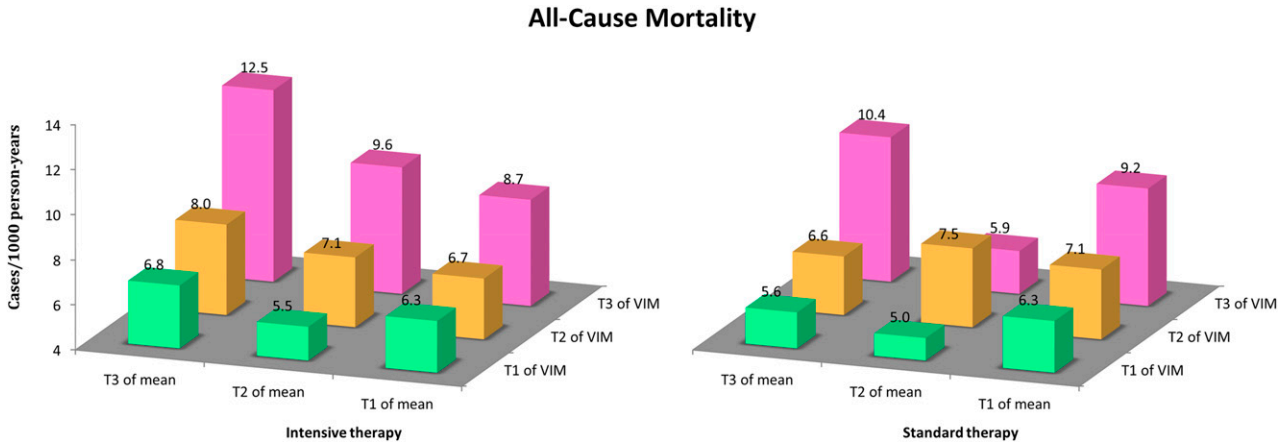

Figure 1—Cross-tabulation analysis of mean and variability. As the tertiles (T) of HbA_{1c} mean and HbA_{1c} VIM increased, the incidence of all-cause mortality increased significantly. The third tertile of HbA_{1c} VIM combined with HbA_{1c} mean had the highest incidence of all-cause mortality.

was the first large-scale study to report the effects of variability in both HbA_{1c} and fasting glucose on a variety of all-cause mortality in type 2 diabetes, including macrovascular events (27). However, the mean number of HbA_{1c} measurements per participant was only five. In this ACCORD population, a mean number of nine measurements of HbA_{1c} in a large-scale clinical trial study allowed assessment of the prognostic significance of HbA_{1c} variability separately in the standard-therapy and intensive-therapy groups. In the intensively treated group, the cross-tabulation analysis shows very clear results: the greater the long-term variability, the higher the incidence of all-cause mortality, regardless of the HbA_{1c}. In addition, this incidence increases with worsening HbA_{1c}. Most interestingly in this study, we found that HbA_{1c} variability combined with HbA_{1c} mean conferred increased risk for all-cause mortality only in the intensive-therapy group, which may be one of the explanations of the higher risk for all-cause mortality among intensive-therapy participants in the ACCORD study.

Going "beyond HbA_{1c}" is an important focus of the current investigation (14). Most traditional clinical trials focus on HbA_{1c} as the definitive measure of efficacy of an intervention. However, mean HbA_{1c} just reflects average glycemia derived without regard to glycemic variability, which is associated with higher risk of hypoglycemia on average (29). Visit-to-visit glycemic variability might be an important confounder for glycemia control and long-term prognosis and should be considered in the management of diabetes.

Our study should be interpreted within the context of its strengths and limitations. The strengths of our study include a large number of high-risk patients and a large number of HbA_{1c} measures, which enable us to accurately calculate HbA_{1c} variability. We used three variability indices, which enable us to study HbA_{1c} variability more comprehensively. The variability index, VIM, can diminish the tight correlation between the CV and mean and was more suitable for the mean and variability cross-tabulation analysis.

The analyses also have limitations. The ACCORD study used HbA_{1c} rather than glucose as the target and evaluation indices, and glucose was not recorded at every visit, so in this study we only focus on HbA_{1c}. Because of the post hoc nature of the analysis and the highly selected study population, which included patients at high risk of CVD, the results should be extended to real-world studies including patients with type 2 diabetes having a variety of risk characteristics.

Conclusion

Our study confirmed that long-term visit-to-visit variability in HbA_{1c} was a strong predictor of a variety of all-cause mortality. HbA_{1c} variability combined with HbA_{1c} mean conferred an increased risk for all-cause mortality in the intensive-therapy group in the ACCORD trial.

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References

1. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ 2000;321:405–412
2. Khaw KT, Wareham N. Glycated hemoglobin as a marker of cardiovascular risk. Curr Opin Lipidol 2006;17:637–643
3. Wright AK, Kontopantelis E, Emsley R, et al. Life expectancy and cause-specific mortality in type 2 diabetes: a population-based cohort study quantifying relationships in ethnic subgroups. Diabetes Care 2017;40:338–345
4. Tian J, Sheng CS, Sun W, et al. Effects of high blood pressure on cardiovascular disease events among Chinese adults with different glucose metabolism. Diabetes Care 2018;41:1895–1900
5. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
6. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
7. Hemmingsen B, Lund SS, Gluud C, et al. Intensive glycaemic control for patients with

type 2 diabetes: systematic review with meta-analysis and trial sequential analysis of randomised clinical trials. BMJ 2011;343:d6898
8. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
9. Jang JY, Moon S, Cho S, Cho KH, Oh CM. Visit-to-visit HbA1c and glucose variability and the risks of macrovascular and microvascular events in the general population. Sci Rep 2019;9:1374
10. Takao T, Matsuyama Y, Yanagisawa H, Kikuchi M, Kawazu S. Association between HbA1c variability and mortality in patients with type 2 diabetes. J Diabetes Complications 2014;28:494–499
11. Luk AO, Ma RC, Lau ES, et al. Risk association of HbA1c variability with chronic kidney disease and cardiovascular disease in type 2 diabetes: prospective analysis of the Hong Kong Diabetes Registry. Diabetes Metab Res Rev 2013;29:384–390
12. Penno G, Solini A, Bonora E, et al.; Renal Insufficiency And Cardiovascular Events Study Group. 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 2013;36:2301–2310
13. Skriver MV, Sandbæk A, Kristensen JK, Støvring H. Relationship of HbA1c variability, absolute changes in HbA1c, and all-cause mortality in type 2 diabetes: a Danish population-based prospective observational study. BMJ Open Diabetes Res Care 2015;3:e000060
14. Bloomgarden Z. Beyond HbA1c, second take. J Diabetes 2019;11:416–417
15. Critchley JA, Carey IM, Harris T, DeWilde S, Cook DG. Variability in glycated hemoglobin and risk of poor outcomes among people with type 2 diabetes in a large primary care cohort study. Diabetes Care 2019;42:2237–2246
16. Echouffo-Tcheugui JB, Zhao S, Brock G, Matsouaka RA, Kline D, Joseph JJ. Visit-to-visit glycemic variability and risks of cardiovascular events and all-cause mortality: the ALLHAT study. Diabetes Care 2019;42:486–493
17. Gerstein HC, Miller ME, Genuth S, et al.; ACCORD Study Group. Long-term effects of intensive glucose lowering on cardiovascular outcomes. N Engl J Med 2011;364:818–828
18. Buse JB, Bigger JT, Byington RP, et al.; ACCORD Study Group. Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial: design and methods. Am J Cardiol 2007;99:21i–33i
19. Gerstein HC, Riddle MC, Kendall DM, et al.; ACCORD Study Group. Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99:34i–43i
20. Rothwell PM, Howard SC, Dolan E, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. Lancet 2010;375:895–905
21. Mena L, Pintos S, Queipo NV, Aizpúrua JA, Maestre G, Sulbarán T. A reliable index for the prognostic significance of blood pressure variability. J Hypertens 2005;23:505–511
22. Rodríguez-Segade S, Rodríguez J, García López JM, Casanueva FF, Camiña F. Intrapersonal HbA_{1c} variability and the risk of progression of nephropathy in patients with type 2 diabetes. Diabet Med 2012;29:1562–1566
23. Lin CC, Chen CC, Chen FN, et al. Risks of diabetic nephropathy with variation in hemoglobin A1c and fasting plasma glucose. Am J Med 2013;126:1017.e1–1017.e10
24. Ma WY, Li HY, Pei D, et al. Variability in hemoglobin A1c predicts all-cause mortality in patients with type 2 diabetes. J Diabetes Complications 2012;26:296–300
25. 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 2015;38:2354–2369
26. Zhou JJ, Schwenke DC, Bahn G, Reaven P; VADT Investigators. Glycemic variation and cardiovascular risk in the Veterans Affairs Diabetes Trial. Diabetes Care 2018;41:2187–2194
27. 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 2014;37:2359–2365
28. Sun B, He F, Gao Y, et al. 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. Endocrine 2019;64:536–543
29. Zhou JJ, Koska J, Bahn G, Reaven P. Glycaemic variation is a predictor of all-cause mortality in the Veteran Affairs Diabetes Trial. Diab Vasc Dis Res 2019;16:178–185