Clinical Research Article

Association of HbA1c With All-cause Mortality Across Varying Degrees of Glycemic Variability in Type 2 Diabetes

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Abstract

Context: The interaction of glycated hemoglobin A1c (HbA1c) and glycemic variability in relation to diabetes-related outcomes remains unknown.

Objective: To evaluate the relationship between HbA1c and all-cause mortality across varying degrees of glycemic variability in patients with type 2 diabetes.

Design, Setting, and Patients: This was a prospective study conducted in a single referral center. Data of 6090 hospitalized patients with type 2 diabetes was analyzed. Glucose coefficient of variation [coefficient of variation (CV)] was obtained as the measure of glycemic variability by using continuous glucose monitoring for 3 days. Cox proportional hazards regression models were used to estimate hazard ratios and 95% CIs for all-cause mortality.

Results: During a median follow-up of 6.8 years, 815 patients died. In patients with the lowest and middle tertiles of glucose CV, HbA1c ≥ 8.0% was associated with 136% (95% CI 1.46-3.81) and 92% (95% CI 1.22-3.03) higher risks of all-cause mortality, respectively, as compared with HbA1c 6.0%-6.9%, after adjusting for confounders. However, a null association of HbA1c with mortality was found in patients with the highest tertile of glucose CV.

Conclusions: HbA1c may not be a robust marker of all-cause mortality in patients with high degree of glycemic variability. New metrics of glycemic control may be needed in these individuals to achieve better diabetes management.
Diabetes is one of the fastest growing public health problems in both developing and developed countries (1). Much of the burden of diabetes is attributable to microvascular and macrovascular complications. Concerning diabetes management, glycated hemoglobin A1c (HbA1c) has been accepted as the most important surrogate marker for diabetic complications and the gold standard for long-term glycemic control. A target value of HbA1c below 7% is recommended by most guidelines published to date to minimize the risk of adverse outcomes (2-4). However, it is increasingly recognized that HbA1c may not be an optimal marker for the quality of glycemic control. From the perspective of clinical practice, it is noted that HbA1c does not provide enough information (eg, hyperglycemia and hypoglycemia) to inform the adjustment of treatment plans. Moreover, the use of HbA1c may sometimes be misleading (5), which is evident in patients with a high degree of glycemic variability (GV). This observation raises the question whether HbA1c is a valid marker for all groups of patients with type 2 diabetes. To date, no outcome-based study has tried to address this issue.

As an important component of dysglycemia, GV has attracted a lot of attention recently. Mechanistic investigations indicated that glucose swings may induce oxidative stress and subsequent endothelial dysfunction (6-9), which are key players in the development of vascular complications of diabetes. Numerous observational studies also provided evidence on the relationship between GV and diabetes-related outcomes (10-12). However, it is not known if HbA1c can predict the risk of diabetes-related outcomes across a wide range of GV. Therefore, the aim of the present study was to investigate the interaction between HbA1c and GV with the risk of all-cause mortality among patients with type 2 diabetes.

**Methods**

**Study Population**

We used data from the INDices of contiNuous Glucose monitoring and adverse Outcomes of diabetes (INDIGO) study (13). The ongoing INDIGO study aims to prospectively recruit inpatients admitted to the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People’s Hospital from January 2005. Patients who enrolled from January 2005 to December 2015 and fulfilled the following criteria were included in the analysis: (1) age ≥ 18 years with the diagnosis of type 2 diabetes; (2) a stable glucose-lowering regimen for the previous 3 months; (3) complete data on HbA1c and continuous glucose monitoring (CGM) parameters; and (4) a citizen of Shanghai, China. We excluded those with other types of diabetes (eg, gestational diabetes or type 1 diabetes), and those who had experienced severe and recurrent hypoglycemic events within the previous 3 months. Subjects included in the final analysis were admitted to the hospital for the evaluation of glucose control and diabetes-related complications and comorbidities but not for other specific reasons such as diabetic ketoacidosis. All patients provided written informed consent. The study protocol was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People’s Hospital and complied with the principles of the Helsinki Declaration.

**Measurements**

Patients’ information on date of birth, sex, age of diabetes diagnosis, smoking status (current smoking or not), history of cancer and cardiovascular disease (CVD; angina, coronary heart disease, or stroke), and medication prescriptions such as antihypertensive drugs, glucose-lowering drugs, and lipid-lowering drugs was collected through a standardized electronic inpatient medical record data collection form. At admission, trained doctors measured height, weight, and blood pressure using a standard protocol. Height and weight were measured to the nearest 0.1 cm using a stadiometer with light clothing and without shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured 3 times using a standard mercury sphygmomanometer after 5 min of sitting, and the measurements were averaged. Blood samples were drawn in the next morning after hospital admission with at least 10-h fasting. HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein cholesterol, and triglycerides were assayed as previously described (13).

**Assessment of CGM Parameters**

A blinded CGM system (CGMS GOLD, Medtronic Inc, Northridge, CA, USA) was used for subcutaneous interstitial glucose monitoring. The sensor of the CGM system was inserted on the first day during hospital admission and removed after 72 h, generating a daily record of 288 continuous sensor values. At least 4 capillary blood glucose readings per day were measured by a SureStep blood glucose meter (LifeScan, Milpitas, CA, USA) to calibrate...
the CGM system. Glucose coefficient of variation (CV) was calculated as the measure of GV. Time in range (TIR) was defined as the percentage of time in the target glucose range of 3.9 to 10.0 mmol/L during a 24-h period. Time above ranges [TARs; TAR > 140 mg/dL (TAR>140), TAR > 180 mg/dL (TAR>180), and TAR > 250 mg/dL (TAR>250)], and time below ranges [TBRs; TBR < 54 mg/dL (TBR<54), and TBR < 70 mg/dL (TBR<70)] were also ascertained. During the CGM period, all participants adhered to a standard diet, as previously reported (14).

**Prospective Follow-up**

Causes and time of death were obtained from the database of the Shanghai Municipal Center for Disease Control and Prevention and were linked with study data through the personal identification number. The death causes were identified with the use of the codes in the *International Classification of Diseases, 10th Revision*. The rate of missing death events in Shanghai was 0.7‰ (T. Xia and J. Zhou, oral communication, September 2012). We used chart review to evaluate the confirmation of death (COD) via the Shanghai adaption of the Medical Data Audit Form. Trained physicians have reviewed the medical records of a death event and have reassigned the COD, which provided a gold standard to measure the quality of routine COD data. The death events identified by Shanghai Civil Registration Vital Statistics routine monitoring were thus reported with high sensitivity and specificity of 85.7% and 90.0%, respectively. All patients were followed up until a death event occurred or until December 31, 2018, whichever occurred first.

**Statistical Analysis**

The trends of continuous variables across the tertiles of glucose CV were assessed using linear polynomial contrasts in an analysis of variance for normally distributed variables and the Jonckheere-Terpstra test for nonnormally distributed data. The Cochran-Armitage trend test was used to examine the trends of rates across groups. The correlations between glucose metrics were evaluated by Spearman’s correlation coefficients. The Cox proportional hazard model was used to estimate the hazard ratio (HR) and 95% CI of HbA1c or other glycemic metrics on all-cause mortality across CV tertiles. HbA1c was categorized into 4 groups (<6.0%, 6.0%-6.9%, 7.0%-7.9%, and ≥8.0%). HbA1c 6.0%-6.9% was selected as the reference group, as our previous study revealed a J-shaped association of HbA1c with all-cause mortality in the same population, with HbA1c 6.0%-6.9% conferring minimal risk of death (13). Three different models were used in the analyses. Covariates in Model 1 included age and sex. In Model 2, we additionally adjusted for diabetes duration, BMI, systolic blood pressure, triglyceride, HDL cholesterol, low-density lipoprotein cholesterol, current smoking status, history of cancer, and history of cardiovascular diseases. Model 3 represented the fully adjusted model, where we additionally adjusted for the use of concomitant medications including aspirin, statins, insulin, oral hypoglycemic agents, and antihypertensive drugs. The potential interactions between glucose CV and glycemic metrics including HbA1c were evaluated by comparing the log-likelihood statistics of models that included interaction terms and models without interaction terms. A P-value of < 0.05 (2-tailed) was considered statistically significant. Statistical analyses were performed using the SPSS software version 17.0 (SPSS Inc, Chicago, IL, USA).

**Results**

A total of 6090 participants were finally included into the analysis. Table 1 shows baseline characteristics of participants stratified by the tertiles of glucose CV (≤21.5%, 21.6%-28.9%, and ≥28.9%). Age, diabetes duration, HDL cholesterol, HbA1c, and the use of insulin and aspirin were positively associated with glucose CV, and BMI, triglycerides, and the use of oral hypoglycemic agents and antihypertensive drugs were inversely associated with glucose CV.

During a median follow-up of 6.8 years (43 108.9 total person-years), 815 people died. As illustrated in Figure 1, the crude mortality rates displayed a similar and obvious pattern in patients with the lowest and middle glucose CV tertiles, where the lowest mortality rate across HbA1c categories (<6.0%, 6.0%-6.9%, 7.0%-7.9%, and ≥8.0%) was observed in HbA1c 6.0%-6.9%. However, the pattern was less pronounced in those with the highest glucose CV tertile. In the total population, the multivariable-adjusted (model 3) HRs of all-cause mortality associated with HbA1c levels (<6.0%, 6.0%-6.9%, 7.0%-7.9%, and ≥8.0%) were 1.64 (95% CI 1.07-2.49), 1.00, 1.37 (95% CI 1.03-1.82), and 1.80 (95% CI 1.40-2.31), respectively (Table 2). In patients with the lowest and middle tertiles of glucose CV, HbA1c ≥ 8.0% was related to 136% (HR 2.36, 95% CI 1.46-3.81) and 92% (HR 1.92, 95% CI 1.22-3.03) higher risk of all-cause mortality as compared with HbA1c 6.0%-6.9% in the fully adjusted model, respectively. However, the 4 categories of HbA1c did not differ in the risk of all-cause mortality in subjects with the highest tertile of glucose CV. A significant interaction between HbA1c and CV (P < 0.05) was observed in Model 2 but not in Models 1 and 3 (both P > 0.10).

In contrast to HbA1c, after multivariable adjustment (Model 3), each 10% decrease in TIR was related to 12%
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Higher risk of all-cause mortality, while each 10% increment in TAR>140, TAR>180, and TAR>250 was associated with 11% (HR 1.11, 95% CI 1.04-1.19), 11% (HR 1.11, 95% CI 1.04-1.18), and 14% (HR 1.14, 95% CI 1.04-1.25) heightened risks of all-cause mortality among patients with the highest tertile of glucose CV, respectively (Table 3).

Concerning the effect of glucose CV on mortality risk, a significant association of glucose CV with all-cause mortality was only observed in individuals with HbA1c 6.0%-6.9%. Specially, relative to patients with the lowest tertile of glucose CV, the risk of mortality was increased by 15% (HR 1.15, 95% CI 0.63-2.11) and 89% (HR 1.89, 95% CI 1.06-3.35) in the middle and highest tertiles of glucose CV (P for trend = 0.027, Model 3) (Table 4).

Table 1. Characteristics of participants by tertiles of glucose CV among patients with type 2 diabetes

| Characteristics | Total | Tertile 1 | Tertile 2 | Tertile 3 | P for trend |
|-----------------|-------|----------|----------|----------|-------------|
| Participants, n | 6090  | 2017     | 2060     | 2013     | /           |
| Person-years    | 43108.9 | 14391.6 | 14438.8 | 14278.5 | /           |
| Age, years      | 61.7 ± 11.9 | 60.8 ± 12.5 | 61.3 ± 11.6 | 62.9 ± 11.4 | <0.001 |
| Men, n (%)      | 3326 (54.6) | 1044 (51.8) | 1170 (56.8) | 1112 (55.2) | 0.026 |
| Diabetes duration, years | 10 (4-15) | 8 (3-13) | 10 (4-14) | 10 (4-15) | <0.001 |
| SBP, mmHg       | 132.9 ± 16.9 | 133.1 ± 17.1 | 132.5 ± 16.6 | 133.0 ± 17.0 | 0.856 |
| DBP, mmHg       | 79.7 ± 9.5 | 80.1 ± 9.8 | 79.6 ± 9.2 | 79.5 ± 9.3 | 0.057 |
| Body mass index, kg/m² | 24.9 ± 3.5 | 25.5 ± 3.6 | 24.9 ± 3.4 | 24.3 ± 3.4 | <0.001 |
| Total cholesterol, mmol/L | 4.7 ± 1.2 | 4.8 ± 1.3 | 4.7 ± 1.2 | 4.7 ± 1.1 | 0.225 |
| Triglycerides, mmol/L | 1.4 (0.9-2.0) | 1.5 (1.1-2.2) | 1.4 (1.0-2.1) | 1.2 (0.8-1.7) | <0.001 |
| HDL cholesterol, mmol/L | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.3 | 1.2 ± 0.3 | <0.001 |
| LDL cholesterol, mmol/L | 2.9 ± 0.9 | 2.9 ± 0.9 | 2.9 ± 1.0 | 3.0 ± 1.0 | 0.613 |
| HbA1c, %        | 8.9 ± 2.2 | 8.5 ± 2.1 | 8.8 ± 2.1 | 9.3 ± 2.3 | <0.001 |
| History of CVD, n (%) | 1299 (21.3) | 430 (21.3) | 418 (20.3) | 451 (22.4) | 0.401 |
| History of cancer, n (%) | 279 (4.6) | 80 (4.0) | 106 (5.1) | 93 (4.6) | 0.321 |
| Current smoker, n (%) | 1441 (23.7) | 446 (22.1) | 529 (25.7) | 466 (23.1) | 0.438 |
| CGM parameter  |
| Glucose CV, %   | 25.8 ± 8.4 | 17.0 ± 3.2 | 25.1 ± 2.1 | 35.2 ± 5.4 | <0.001 |
| TBR<54, %       | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.0 (0.0-0.0) | 0.0 (0.0-0.9) | <0.001 |
| TBR<70, %       | 0.0 (0.0-1.2) | 0.0 (0.0-0.0) | 0.0 (0.0-0.5) | 1.2 (0.0-5.2) | <0.001 |
| TAR>140, %      | 62.9 (41.8-81.9) | 72.9 (37.7-93.4) | 64.4 (43.6-81.6) | 57.3 (42.7-70.9) | <0.001 |
| TAR>180, %      | 29.5 (13.4-50.7) | 22.6 (4.9-57.3) | 28.8 (14.1-49.0) | 33.0 (20.3-47.9) | <0.001 |
| TAR>250, %      | 4.0 (0.0-1.30) | 0.0 (0.0-5.8) | 3.3 (0.0-10.8) | 9.2 (3.6-18.5) | <0.001 |
| TIR, %          | 64.5 ± 24.6 | 66.6 ± 31.2 | 65.5 ± 23.1 | 61.3 ± 17.1 | <0.001 |
| Medication, n (%)  |
| Oral hypoglycemic drugs | 4303 (70.7) | 1534 (76.1) | 1472 (71.5) | 1297 (64.4) | <0.001 |
| Insulin         | 4072 (66.9) | 1080 (53.5) | 1378 (66.9) | 1614 (80.2) | <0.001 |
| Anti-hypertensive drugs | 3308 (54.3) | 1145 (56.8) | 1102 (53.5) | 1061 (52.7) | 0.010 |
| Aspirin         | 2870 (47.1) | 909 (45.1) | 982 (47.7) | 979 (48.6) | 0.023 |
| Statins         | 2349 (38.6) | 773 (38.3) | 795 (38.6) | 781 (38.8) | 0.757 |

Data shown are mean ± SD, median (interquartile range) or number (percentage) unless otherwise indicated.

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL cholesterol, high-density lipoprotein cholesterol; LDL cholesterol, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TBR<54, time below range (<54 mg/dL); TBR<70, time below range (<70 mg/dL); TAR>140, time above range (>140 mg/dL); TAR>180, time above range (>180 mg/dL); TAR>250, time above range (>250 mg/dL); TIR, time in range; HbA1c, glycated hemoglobin A1c.
In a large cohort of inpatients with type 2 diabetes, we explored the impact of HbA1c on all-cause mortality across varying degrees of GV, as measured by glucose CV through CGM. We found that the association of HbA1c with all-cause mortality seemed to be weakened in individuals with the highest tertile of glucose CV, suggesting that patients with a high degree of GV may not benefit from the measurement of HbA1c as much as others.

There is compelling evidence supporting the link between HbA1c and diabetes-related outcomes (15-18). Nevertheless, given that HbA1c reflects the mean glucose over the previous 2 to 3 months, a patient with an HbA1c “under control” could have concomitant uncontrolled hyperglycemia and hypoglycemia. The former is clearly detrimental to micro- and macrovasculatures (19,20), while the latter is related to the quality of life (21), dementia (22), CVD events (23), and mortality (24).

Therefore, although HbA1c is undoubtedly a valid marker for diabetic complications in the general population with diabetes, it may not adequately address the burden of adverse outcomes in certain patient groups. In support of this notion, some clinical trials targeting HbA1c to specific goals, including ACCORD (25), ADVANCE (18), and VADT (26), did not show improved CVD end points in patients with advanced type 2 diabetes. Of note, no previous studies have investigated whether GV modifies the relationship between HbA1c and clinical outcomes among patients with type 2 diabetes. Our study demonstrated a weaker association of HbA1c with all-cause mortality in patients with relatively high levels of glucose fluctuations than in those with stable glucose values, suggesting that other glucose metrics in addition to HbA1c are needed for better diabetes care.

### Table 2. Hazard ratios of all-cause mortality according to categories of HbA1c among patients with type 2 diabetes by total samples and across glucose CV tertiles

| HbA1c  | <6.0% | 6.0%-6.9% | 7.0%-7.9% | ≥8.0% |
|--------|-------|-----------|-----------|-------|
| Total samples |        |           |           |       |
| Participants/deaths, n | 291/33 | 988/83 | 1152/128 | 3659/571 |
| Person-years | 1996.6 | 7114.0 | 7976.1 | 26022.3 |
| Adjusted HRs (95% CIs) |     |           |           |       |
| Model 1 | 1.51 (1.00-2.29) | 1 (reference) | 1.42 (1.07-1.88) | 2.06 (1.62-2.61) |
| Model 2 | 1.62 (1.06-2.46) | 1 (reference) | 1.40 (1.06-1.86) | 2.02 (1.59-2.56) |
| Model 3 | 1.64 (1.07-2.49) | 1 (reference) | 1.37 (1.03-1.82) | 1.80 (1.40-2.31) |

| Patients with tertile 1 of glucose CV |        |           |           |       |
| Participants/Deaths, n | 132/14 | 407/24 | 408/47 | 1070/164 |
| Person-years | 932.6 | 2988.1 | 2805.7 | 7665.3 |
| Adjusted HRs (95% CIs) |     |           |           |       |
| Model 1 | 1.98 (0.99-3.95) | 1 (reference) | 2.20 (1.31-3.68) | 3.11 (1.97-4.90) |
| Model 2 | 2.11 (1.05-4.25) | 1 (reference) | 2.09 (1.24-3.53) | 2.82 (1.78-4.48) |
| Model 3 | 1.98 (0.98-4.00) | 1 (reference) | 1.99 (1.18-3.36) | 2.36 (1.46-3.81) |

| Patients with tertile 2 of glucose CV |        |           |           |       |
| Participants/deaths, n | 100/11 | 330/25 | 409/32 | 1221/176 |
| Person-years | 663.9 | 2337.4 | 2847.0 | 8590.5 |
| Adjusted HRs (95% CIs) |     |           |           |       |
| Model 1 | 1.68 (0.82-3.45) | 1 (reference) | 1.09 (0.64-1.87) | 2.11 (1.36-3.26) |
| Model 2 | 1.94 (0.94-4.02) | 1 (reference) | 1.03 (0.60-1.76) | 2.05 (1.32-3.18) |
| Model 3 | 1.99 (0.96-4.12) | 1 (reference) | 1.04 (0.61-1.79) | 1.92 (1.22-3.03) |

| Patients with tertile 3 of glucose CV |        |           |           |       |
| Participants/deaths, n | 59/8 | 251/34 | 335/49 | 1368/231 |
| Person-years | 400.1 | 1788.6 | 2323.4 | 9766.4 |
| Adjusted HRs (95% CIs) |     |           |           |       |
| Model 1 | 1.21 (0.53-2.72) | 1 (reference) | 1.20 (0.78-1.87) | 1.40 (0.97-2.00) |
| Model 2 | 1.28 (0.56-2.92) | 1 (reference) | 1.20 (0.77-1.86) | 1.40 (0.98-2.02) |
| Model 3 | 1.29 (0.57-2.96) | 1 (reference) | 1.22 (0.78-1.91) | 1.38 (0.94-2.02) |

Model 1 adjusted for age and sex; Model 2 further adjusted for diabetes duration, smoking, body mass index, systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of cancer, and history of cardiovascular diseases; Model 3 adjusted for the covariates in Model 2 plus the use of aspirin, statins, oral hypoglycemic agents, insulin, and antihypertensive drugs.

Abbreviations: CV, coefficient of variation; HbA1c, glycated hemoglobin A1c; HR, hazard ratio.

### Discussion

In a large cohort of inpatients with type 2 diabetes, we explored the impact of HbA1c on all-cause mortality across varying degrees of GV, as measured by glucose CV through CGM. We found that the association of HbA1c with all-cause mortality seemed to be weakened in individuals with the highest tertile of glucose CV, suggesting that patients with a high degree of GV may not benefit from the measurement of HbA1c as much as others.

There is compelling evidence supporting the link between HbA1c and diabetes-related outcomes (15-18). Nevertheless, given that HbA1c reflects the mean glucose over the previous 2 to 3 months, a patient with an HbA1c “under control” could have concomitant uncontrolled hyperglycemia and hypoglycemia. The former is clearly detrimental to micro- and macrovasculatures (19,20), while the latter is related to the quality of life (21), dementia (22), CVD events (23), and mortality (24). Therefore, although HbA1c is undoubtedly a valid marker for diabetic complications in the general population with diabetes, it may not adequately address the burden of adverse outcomes in certain patient groups. In support of this notion, some clinical trials targeting HbA1c to specific goals, including ACCORD (25), ADVANCE (18), and VADT (26), did not show improved CVD end points in patients with advanced type 2 diabetes. Of note, no previous studies have investigated whether GV modifies the relationship between HbA1c and clinical outcomes among patients with type 2 diabetes. Our study demonstrated a weaker association of HbA1c with all-cause mortality in patients with relatively high levels of glucose fluctuations than in those with stable glucose values, suggesting that other glucose metrics in addition to HbA1c are needed for better diabetes care.
Table 3. Associations of CGM metrics with all-cause mortality across tertiles of glucose CV

| CGM metrics/glucose CV | Adjusted HRs (95% CIs)³ | Model 1 | Model 2 | Model 3 |
|------------------------|------------------------|---------|---------|---------|
| Time in range          |                        |         |         |         |
| Tertile 1              | 1.08 (1.04-1.12)        | 1.06 (1.02-1.11) | 1.03 (0.98-1.08) |
| Tertile 2              | 1.09 (1.03-1.15)        | 1.07 (1.02-1.13) | 1.05 (0.99-1.12) |
| Tertile 3              | 1.13 (1.06-1.21)        | 1.12 (1.05-1.20) | 1.12 (1.04-1.20) |
| P for interaction      | <0.025                 | <0.025  | <0.025  |
| Time above range (>140 mg/dL) |            |         |         |         |
| Tertile 1              | 1.10 (1.05-1.15)        | 1.08 (1.03-1.14) | 1.05 (1.00-1.11) |
| Tertile 2              | 1.09 (1.03-1.15)        | 1.07 (1.01-1.13) | 1.05 (0.99-1.11) |
| Tertile 3              | 1.12 (1.06-1.19)        | 1.11 (1.04-1.18) | 1.11 (1.04-1.19) |
| P for interaction      | >0.10                  | >0.25   | >0.25   |
| Time above range (>180 mg/dL) |            |         |         |         |
| Tertile 1              | 1.08 (1.04-1.12)        | 1.06 (1.01-1.10) | 1.02 (0.98-1.07) |
| Tertile 2              | 1.09 (1.03-1.14)        | 1.07 (1.02-1.13) | 1.05 (0.99-1.11) |
| Tertile 3              | 1.12 (1.06-1.19)        | 1.11 (1.05-1.19) | 1.11 (1.04-1.18) |
| P for interaction      | <0.05                  | <0.05   | <0.05   |
| Time above range (>250 mg/dL) |            |         |         |         |
| Tertile 1              | 1.10 (1.02-1.19)        | 1.06 (0.98-1.16) | 1.01 (0.92-1.10) |
| Tertile 2              | 1.14 (1.04-1.24)        | 1.10 (1.01-1.21) | 1.07 (0.98-1.18) |
| Tertile 3              | 1.16 (1.07-1.26)        | 1.15 (1.06-1.26) | 1.14 (1.04-1.25) |
| P for interaction      | >0.10                  | >0.10   | >0.10   |
| Time below range (<54 mg/dL) |            |         |         |         |
| Tertile 1              | 0.17 (0.01-2.72)        | 0.23 (0.02-3.15) | 0.30 (0.03-3.39) |
| Tertile 2              | 0.92 (0.72-1.17)        | 0.93 (0.73-1.18) | 0.95 (0.77-1.18) |
| Tertile 3              | 0.97 (0.93-1.01)        | 0.97 (0.93-1.02) | 0.97 (0.92-1.01) |
| P for interaction      | <0.05                  | <0.05   | <0.05   |
| Time below range (<70 mg/dL) |            |         |         |         |
| Tertile 1              | 0.98 (0.90-1.07)        | 0.99 (0.92-1.06) | 0.99 (0.94-1.05) |
| Tertile 2              | 0.98 (0.92-1.04)        | 0.99 (0.93-1.05) | 0.99 (0.94-1.05) |
| Tertile 3              | 0.98 (0.96-1.01)        | 0.98 (0.96-1.01) | 0.98 (0.96-1.01) |
| P for interaction      | >0.50                  | >0.50   | >0.25   |

Model 1 adjusted for age and sex; Model 2 further adjusted for diabetes duration, smoking, body mass index, systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of cancer, and history of cardiovascular diseases; Model 3 adjusted for the covariates in Model 2 plus the use of aspirin, statins, oral hypoglycemic agents, insulin, and antihypertensive drugs.

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; HR, hazard ratio.

³Calculated for each 10% decrease in TIR, 10% increase in time above range and 1% increase in time below range.

To date, CGM has been demonstrated to be effective in glucose management in patients with both type 1 and type 2 diabetes (27-29). Unfortunately, due to the high cost of CGM, it is used only in a small portion of patients with diabetes, especially in those with type 1 diabetes who have been struggling to achieve a specific HbA1c. Findings of our study implied that, apart from a useful tool for health education and guiding therapy changes, CGM could be implemented to assess GV and therefore to evaluate the suitability of HbA1c in diabetes management in certain subjects. Furthermore, we found consistent associations of TIR and TARs with all-cause mortality in patients with a high degree of GV, suggesting that CGM may provide additional information over HbA1c in predicting health outcomes in this subset of diabetic patients.

The results of the present study need to be interpreted within the context of several limitations. First, 3 days of CGM were used in the study, while 2 to 4 weeks of monitoring may be needed to robustly assess the actual GV (30,31). In addition, all patients received standard diets during CGM. Therefore, the glucose profiles obtained in this study may not represent the patients’ quality of glucose control in the real life, and the CGM parameters, including CV, should not be directly compared with other studies. However, this proof-of-concept study may provide insights into the potential caveats of HbA1c in predicting diabetes-related outcomes. Second, the data on socioeconomic and lifestyle were not available in the present study, and residual confounding was almost inevitable. Third, data on HbA1c was based on 1 measurement (ie, baseline), which was less precise than taking average HbA1c.
values during the study follow-up, and the investigation on the effect of visit-to-visit variability of HbA1c on mortality risk was precluded. Fourth, the data on the smoking status and history of CVD and cancer were collected by self-report, which can lead to potential misclassification bias. Since misclassification tends to bias the results to the null, our study may have underestimated the association between glucose CV and mortality. Finally, the subjects who enrolled in the current study were inpatients with type 2 diabetes admitted to a single center. To what degree these results could be generalized to other populations is unclear.

In conclusion, the relationship between HbA1c and all-cause mortality seemed to be blunted in diabetic patients with a relatively high degree of GV, suggesting that new markers of glycemia may be needed in this subset of patients with diabetes for better diabetes management.

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Table 4. Hazard ratios of all-cause mortality according to tertiles of glucose CV among patients with type 2 diabetes by total samples and across HbA1c categories

| HbA1c | Glucose CV | Tertile 1 | Tertile 2 | Tertile 3 | P for trend |
|-------|------------|-----------|-----------|-----------|-------------|
| Total | Model 1 1 (reference) | 1.00 (0.83-1.19) | 1.20 (1.01-1.41) | 0.141 |
|       | Model 2 1 (reference) | 0.99 (0.83-1.19) | 1.17 (0.99-1.39) | 0.229 |
|       | Model 3 1 (reference) | 0.94 (0.78-1.13) | 1.05 (0.88-1.25) | 0.761 |
| <6.0% | Model 1 1 (reference) | 1.29 (0.57-2.93) | 1.34 (0.53-3.37) | 0.489 |
|       | Model 2 1 (reference) | 1.11 (0.47-2.59) | 1.52 (0.58-3.99) | 0.425 |
|       | Model 3 1 (reference) | 1.40 (0.54-3.66) | 1.87 (0.68-5.18) | 0.222 |
| 6.0%-6.9% | Model 1 1 (reference) | 1.40 (0.77-2.52) | 2.27 (1.31-3.93) | 0.003 |
|       | Model 2 1 (reference) | 1.35 (0.75-2.45) | 2.25 (1.29-3.93) | 0.004 |
|       | Model 3 1 (reference) | 1.15 (0.63-2.11) | 1.89 (1.06-3.35) | 0.027 |
| 7.0%-7.9% | Model 1 1 (reference) | 0.71 (0.45-1.11) | 1.22 (0.82-1.84) | 0.343 |
|       | Model 2 1 (reference) | 0.68 (0.43-1.08) | 1.20 (0.78-1.83) | 0.419 |
|       | Model 3 1 (reference) | 0.67 (0.42-1.06) | 1.13 (0.73-1.74) | 0.372 |
| ≥8.0% | Model 1 1 (reference) | 0.95 (0.77-1.18) | 0.98 (0.80-1.20) | 0.907 |
|       | Model 2 1 (reference) | 0.95 (0.77-1.18) | 0.96 (0.78-1.19) | 0.755 |
|       | Model 3 1 (reference) | 0.94 (0.76-1.17) | 0.93 (0.75-1.15) | 0.501 |

Model 1 adjusted for age and sex; Model 2 further adjusted for diabetes duration, smoking, body mass index, systolic blood pressure, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, history of cancer, and history of cardiovascular diseases; Model 3 adjusted for covariates in Model 2 plus the use of aspirin, statins, insulin, oral hypoglycemic agents, and antihypertensive drugs.

Abbreviations: CV, coefficient of variation; HbA1c, glycated hemoglobin A1c.
Disclosure Summary: The authors have nothing to disclose.

Data Availability: Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The correspond- ing authors will on request detail the restrictions and any conditions under which access to some data may be provided.

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