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Association between visit-to-visit HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes

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Abstract

Aim: To investigate the association between visit-to-visit HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes.

Materials and methods: We performed a retrospective cohort study of 29 260 patients with at least four HbA1c measurements obtained within 2 years of their first diagnosis of type 2 diabetes. Different HbA1c variability markers were calculated, including the standard deviation (SD), coefficient of variation (CV) and adjusted SD. Cox proportional hazards regression models were used to estimate the association of these HbA1c variability markers with incident cardiovascular disease.

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AUTHOR CONTRIBUTIONS

YS and JZ contributed equally to this work. LS and GH designed the study. YS, JZ, EN and EGP-H conducted the study and collected the data. YS and JZ performed the analysis. YS, JZ and GH wrote the manuscript. LS, EN, PTK, EGP-H, RH, ANB and SN reviewed and edited the manuscript. GH is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

None declared.

PEER REVIEW

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SUPPORTING INFORMATION

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Results: During a mean follow-up of 4.18 years, a total of 3746 incident cardiovascular disease cases were diagnosed. Multivariate-adjusted hazard ratios for cardiovascular disease across the first, second, third and fourth quartiles of HbA1c SD values were 1.00, 1.30 (95% confidence interval [CI] 1.18–1.42), 1.40 (95% CI 1.26–1.55) and 1.59 (95% CI 1.41–1.77) (*P* for trend <.001), respectively. When we utilized HbA1c CV and adjusted HbA1c SD values as exposures, similar positive associations were observed. HbA1c variability was also associated with the risk of first and recurrent severe hypoglycaemic events. A mediating effect of severe hypoglycaemia was observed between HbA1c variability and incident cardiovascular disease.

Conclusions: Large visit-to-visit HbA1c variability is associated with an increased risk of cardiovascular disease in patients with type 2 diabetes. Severe hypoglycaemia may mediate the association between HbA1c variability and incident cardiovascular disease.

Keywords

cardiovascular disease; severe hypoglycaemic event; visit-to-visit HbA1c variability

1 | INTRODUCTION

The worldwide disease burden associated with diabetes is substantial. Several major causes of death, including cardiovascular disease, are associated with diabetes.[1] Optimal targets for glycaemic measurements, such as fasting plasma glucose, postprandial plasma glucose and HbA1c, are recommended by several professional organizations.[2–4] While fasting plasma glucose and postprandial plasma glucose are both indicators of current glycaemic control, HbA1c is widely used because it can reflect glycaemic levels over a longer period of time (2–3 months). The current guidelines from the American Diabetes Association recommend an HbA1c level of less than 7% as the treatment goal.[2] However, emerging evidence in recent years indicates that glucose excursions or fluctuations may be a better predictor of diabetic complications than single-point glucose levels.[5] Glycaemic variability is defined as the fluctuation of glucose homeostasis over a certain interval of time and is commonly evaluated by visit-to-visit HbA1c variability. Results from several studies have shown that visit-to-visit HbA1c variability may have a major impact on cardiovascular events and all-cause mortality in patients with or without diabetes.[6–8] However, no studies have assessed the potential factors that could mediate the association between visit-to-visit HbA1c variability and the risk of cardiovascular disease. In the present study, we aimed to investigate the association between visit-to-visit HbA1c variability and the risk of cardiovascular disease in patients with type 2 diabetes and find out the potential mediator using data from a large healthcare system to reflect the real-world setting.

2 | MATERIALS AND METHODS

2.1 | Study participants

Data from patients with type 2 diabetes in the Louisiana Experiment Assessing Diabetes outcomes (LEAD) cohort study were obtained through the Research Action for Health Network (REACHnet).[9,10] The dataset included electronic health record data for the study cohort from 1 January 2013 to 30 April 2018. Patients included in this study had no less

than 1 year's worth of data available for analysis and they attended regular check-ups or refilled prescriptions within 1 year before the end of their healthcare membership or the end of the study. For the present study, data from two REACHnet partner health systems (Ochsner Health System and Tulane University) were included in the final pooled analysis. A unique global identifier was used to link records across the two health systems to avoid the duplication of individual patients in the pooled dataset. In total, 9268 out of 258 374 records were identified as duplicates across the two partner health systems. The study and the analysis plan were approved by the Institutional Review Boards (Research Ethics Committees) of the Pennington Biomedical Research Center (2016–064-PBRC), Tulane University (906810) and Ochsner Health System (Ochsner acknowledged Tulane's approval). We did not obtain informed consent from participants involved in our study because we used anonymized data compiled from electronic medical records.

The definition of type 2 diabetes in the present study was formulated according to the SUPREME-DM[11] criteria as follows: (a) one or more of the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) codes and Tenth Revision, Clinical Modification (ICD-10-CM) codes for type 2 diabetes associated with inpatient encounters; (b) two or more ICD codes associated with outpatient encounters on different days within 2 years; (c) a combination of two or more of the following variables associated with outpatient encounters on different days within 2 years: ICD codes, fasting glucose level ≥126 mg/dL, 2-hour glucose level ≥200 mg/dL, random glucose level ≥200 mg/dL, HbA1c ≥ 6.5% and prescription of an antidiabetic medication. A total of 107 562 patients between the ages of 30 and 94 years were identified. Eligible patients also had to have at least four HbA1c measurements obtained within 2 years of their first diagnosis of type 2 diabetes in the healthcare system. We excluded patients with no HbA1c results and also those who had cardiovascular events 1 year prior to and within 2 years after the first date of their type 2 diabetes diagnosis (Figure S1). The final sample for analysis included 29 260 patients with type 2 diabetes (17 392 whites and 11 868 African Americans).

To investigate for the presence of selection bias, we compared patients included in the analysis with those excluded from the analysis (Table S4). Compared with patients with diabetes who were excluded from the present study, the patients that were included in the analysis were of a similar age (66.0 ± 11.6 vs. 66.3 ± 12.5 years of age, respectively). However, there were more African Americans (40.6% vs. 36.2%) and fewer men (45.9% vs. 49.1%) in the group of patients included in our study.

2.2 | Baseline measurements

The National Patient-Centered Clinical Research Network (PCORnet) common data model defines a standard for the organization and representation of data for the PCORnet distributed research network.[12] Patient data for this study conformed to this common data model and included: date of birth; age at diabetes diagnosis; race; ethnicity; sex; encounter dates; weight; height; body mass index (BMI); blood pressure; tobacco use; diagnoses of various diseases and dates of the diagnoses; laboratory test dates; total cholesterol levels; triglyceride levels; high-density lipoprotein (HDL) cholesterol levels; low-density lipoprotein (LDL) cholesterol levels; HbA1c levels; estimated glomerular filtration rate

(eGFR); and the use of medication prescriptions such as antihypertensive drugs, glucose-lowering drugs and lipid-lowering drugs. Using data collected about the patient's self-reported smoking status at each clinic visit, we classified the patients into three groups: current smokers, ever smokers and never smokers. The eGFR was estimated using the Modification of Diet in Renal Disease formula.[13]

2.3 | Follow-up and visit-to-visit HbA1c variability

We created a follow-up database in electronic form using unique patient identifiers. The updated mean value of HbA1c was calculated for each participant within 2 years from the first date of the type 2 diabetes diagnosis. The standard deviation (SD) of HbA1c was calculated for each participant within 2 years from the first date of the type 2 diabetes diagnosis. To minimize any effect of different numbers of HbA1c measurements on the calculated values, an adjusted HbA1c SD was defined according to the formula: adjusted HbA1c SD = SD/√[n/(n−1)].[14] To correct for a larger SD because of higher absolute updated mean values of HbA1c as a normalized measure of variability, the coefficient of variation of HbA1c (HbA1c CV) was calculated as the HbA1c SD divided by the updated mean value of HbA1c prior to conversion to a percentage. To avoid immortal time bias, the baseline date was set as the last date of HbA1c measurement within 2 years following the first date of the type 2 diabetes diagnosis. The average number of HbA1c measurements during the follow-up period was 9.04.

The primary outcomes of our study were cardiovascular events including coronary heart disease and stroke. ICD-9-CM and ICD-10-CM codes were used to identify coronary heart disease (ICD-9-CM codes 410–415 and 429.2; ICD-10-CM codes I20-I26), stroke (ICD-9-CM codes 430–436; ICD-10-CM codes I60-I66) and cardiovascular disease events (ICD-9-CM codes 410–415, 429.2 and 430–436; ICD-10-CM codes I20-I26 and I60-I66). Severe hypoglycaemic episodes were defined by ICD codes 251 and E16. These diagnoses were recorded in the course of routine patient care by the patients' treating clinicians. The duration of follow-up for each cohort member (in person-years) was tabulated from the baseline date to the date of diagnosis of the outcome, death while an inpatient, the date of dropout, loss to follow-up because of discontinuation of the patient's healthcare membership, or 30 April 2018. The diagnosis of cardiovascular events could be made during outpatient, inpatient or emergency encounters. Encounter types documented as 'ambulatory visit' or 'other ambulatory visit' were considered as outpatient encounters, while encounter types documented as 'inpatient', 'emergency department', 'emergency admission to inpatient', 'institutional stay', 'observation stay' and 'institutional consult' were considered as either inpatient or emergency encounters.

2.4 | Statistical analyses

Cox proportional hazards regression was used to estimate hazard ratios (HRs) for incident cardiovascular events according to quartiles of HbA1c SD, HbA1c CV and adjusted HbA1c SD, which were also evaluated as continuous variables (per 1 unit increase for HbA1c SD and adjusted HbA1c SD, and per 10-unit increase for HbA1c CV). These visit-to-visit HbA1c variability indices were included in the models as dummy variables, and the significance of the trend across categories of HbA1c was tested in the same

models by giving an ordinal numeric value for each dummy variable. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions.[15] In general, all proportionality assumptions were appropriate. All analyses were first conducted after adjusting for age, sex and race, and then further for smoking, BMI, systolic blood pressure, non-HDL/HDL ratio, eGFR, insurance type, hypoglycaemic events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications, antiplatelet and anticoagulant medications, and the updated mean value of HbA1c. Cox proportional hazards models and Poisson regression models were used to estimate the association of these HbA1c variability markers with the risk of first and recurrent hospitalization for severe hypoglycaemia. Subgroup analyses were performed in groups of patients with different ages, races, sexes, BMI, baseline HbA1c levels, proportion of patients that had never smoked, and the proportion of patients receiving and not receiving glucose-lowering, lipid-lowering and antihypertensive medications. Further, mediation analysis was performed to quantify the contribution of one specific factor (the independent variable) to the outcome, adjusting for all confounding factors according to Baron and Kenny's steps for mediation.[16] Statistical significance was considered to be P less than .05. All statistical analyses were performed using IBM SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA).

3 | RESULTS

The baseline characteristics of patients grouped into quartiles based on the calculated HbA1c SD values are presented in Table 1. Patients with higher visit-to-visit HbA1c SD values were younger, had a higher BMI and blood pressure, as well as worse lipid profiles. Patients with higher HbA1c SD values were also more probably current smokers, less probable to have Medicare as their primary payer and less probably using antihypertensive and glucose-lowering medications.

During a mean follow-up period of 4.18 years, 3746 participants developed incident cardiovascular disease. Multivariate-adjusted (incorporating the variables of age, race, sex, smoking, BMI, systolic blood pressure, non-HDL/HDL ratio, eGFR, insurance type, hypoglycaemic events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications, and antiplatelet and anticoagulant medications by category differences, as well as the updated mean value of HbA1c) HRs for cardiovascular disease across the first, second, third and fourth quartiles of HbA1c SD values were 1.00, 1.30 (95% confidence interval [CI] 1.18–1.42), 1.40 (95% CI 1.26–1.55) and 1.59 (95% CI 1.41–1.77; P for trend <.001), respectively (Table 2). When we used HbA1c CV and adjusted HbA1c SD values as exposures, similar positive associations with the risk of cardiovascular disease were found. Multivariate-adjusted HRs for cardiovascular disease were 1.18 (95% CI 1.08–1.27) and 1.30 (95% CI 1.20–1.40) for each 1 SD or 1 adjusted SD increase in HbA1c, respectively, and 1.20 (95% CI 1.15–1.26) for each 10-unit increase in HbA1c CV (Table 2).

During a mean follow-up period of 3.66 years, 2348 incident coronary heart disease cases were diagnosed. Multivariate-adjusted HRs for coronary heart disease across the first, second, third and fourth quartiles of HbA1c SD, HbA1c CV and adjusted HbA1c SD values were, respectively: 1.00, 1.31, 1.40 and 1.71 (P for trend <.001); 1.00, 1.30, 1.46 and 1.65

(*P* for trend <.001); and 1.00, 1.40, 1.42 and 1.71 (*P* for trend <.001; Table 3). When HbA1c SD, HbA1c CV and adjusted HbA1c SD values were examined as continuous variables, the multivariate-adjusted HRs for coronary heart disease were 1.27 (95% CI 1.15–1.37) and 1.32 (95% CI 1.21–1.45) for each 1 SD or 1 adjusted SD increase in HbA1c, respectively, and 1.20 (95% CI 1.12–1.29) for each 10-unit increase in HbA1c CV (Table 3).

There were 1851 new stroke cases during a mean follow-up period of 4.31 years. There were positive associations of HbA1c SD, HbA1c CV and adjusted HbA1c SD values with the risk of stroke (Table 4). The multivariate-adjusted HRs for stroke were 1.30 (95% CI 1.17–1.43) and 1.40 (95% CI 1.26–1.55) for each 1 SD or 1 adjusted SD increase in HbA1c, respectively, and 1.20 (95% CI 1.11–1.30) for each 10-unit increase in HbA1c CV.

When both baseline and mean HbA1c values were used as exposures (Table S1), a significant U-shaped association was observed. Higher baseline and mean HbA1c values, as well as extremely low HbA1c levels, were associated with a higher risk of cardiovascular disease.

When stratified analyses were utilized, the positive association between HbA1c variability markers and the risk of cardiovascular disease was consistent in patients of different ages, races, sexes, BMI, baseline HbA1c levels, patients that have never smoked, and patients receiving and not receiving lipid-lowering and antihypertensive agents (Table 5). However, significant associations between HbA1c variability and cardiovascular disease were not present in patients receiving α-glucosidase inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, meglitinides, thiazolidinediones and sodium-glucose co-transporter-2 (SGLT2) inhibitors.

During a mean follow-up period of 4.43 years, a total of 1211 patients with type 2 diabetes experienced a first hospitalization for severe hypoglycaemia. These patients experienced 0.04 hospitalizations for severe hypoglycaemia events per person-year. Multivariate-adjusted HRs for first hospitalization for severe hypoglycaemia across the first, second, third and fourth quartiles of HbA1c SD values were 1.00, 1.60 (95% CI 1.27–2.01), 2.54 (95% CI 2.04–3.18) and 3.00 (95% CI 2.36–3.82; *P* for trend <.001), respectively (Table S2). When we used HbA1c CV and adjusted HbA1c SD values as exposures, similar positive associations with the risk of first hospitalization for severe hypoglycaemia were found. Multivariate-adjusted HRs for recurrent hospitalization for severe hypoglycaemia across the first, second, third and fourth quartiles of HbA1c SD were 1.00, 1.45 (95% CI 1.30–1.63), 2.52 (95% CI 2.26–2.80) and 3.08 (95% CI 2.75–3.47; *P* for trend <.001), respectively (Table S3). When we used HbA1c CV and adjusted HbA1c SD values as exposures, similar positive associations with the risk of recurrent hospitalization for severe hypoglycaemia were found.

In order to test the mediating effects of severe hypoglycaemic events on the association between HbA1c variability and cardiovascular disease, we performed a mediation analysis. The β1 value of HbA1c CV for the risk of cardiovascular disease was 0.25 (*P* < .001) without severe hypoglycaemic events in the model. The β2 value of HbA1c CV for the risk of severe hypoglycaemic events was 0.49 (*P* < .001). The β3 of HbA1c CV for the risk of

cardiovascular disease was 0.22 ($P < .001$) after controlling for severe hypoglycaemic events (Figure S2). The mediated proportion was calculated as 12.0%.

4 | DISCUSSION

Our study found significant positive associations between different HbA1c variability markers and the risk of coronary heart disease, stroke and cardiovascular disease in patients with type 2 diabetes. These associations may be mediated by the presence of severe hypoglycaemia during the observation period.

Several studies have found that glycaemic variability, especially HbA1c variability, is associated with adverse outcomes and mortality.[6–8,17,18] One systematic review and meta-analysis of 20 studies (seven performed in patients with type 1 diabetes and 13 in patients with type 2 diabetes) published in 2015[19] concluded that HbA1c variability was positively associated with micro- and macrovascular complications and mortality independent of mean HbA1c levels. Among the 13 studies in patients with type 2 diabetes, 11 of them were cohort studies and two were post hoc analyses of randomized controlled trials. Moreover, almost all cohort studies were from Asia (n = 6) or Europe (n = 4), with different study sample sizes (n = 234–11 205); only one study was from the United States and it was limited by a comparatively small sample size (n = 791). The association between glycaemic variability and risk of cardiovascular disease has also been shown in non-diabetic patients.[7] In one Italian study, mean HbA1c levels rather than HbA1c variability were shown to be associated with macrovascular complications.[20] Recently, Li et al. found that higher HbA1c variability is associated with an increased risk of all-cause mortality and cardiovascular events independent of high HbA1c levels, by using real-world data from the UK.[17] Although patients with type 2 diabetes were all newly diagnosed, similar findings were reported. A recent review concluded that the association between glycaemic variability and the risk of cardiovascular disease remains controversial.[18] These inconsistent results may be explained by the use of limited glucose measurements and different study settings. Furthermore, some studies are limited by strict inclusion and exclusion criteria, short follow-up durations, a low incidence of diabetic complications and a failure to include multiple racial groups. Some studies were focused on assessments of pharmaceutical effectiveness and safety.

In the present study, we used data from electronic medical records comprising nearly 30 000 patients with type 2 diabetes. Eligible patients had at least four measurements of HbA1c within 2 years of their first record of type 2 diabetes diagnosis. Those who already had cardiovascular disease during this 2-year period were excluded. These inclusion and exclusion criteria were similar to several post hoc analyses of clinical trials, enhancing the comparability of our results. The present study found positive associations between different HbA1c variability markers and the risk of coronary heart disease, stroke and cardiovascular disease in patients with type 2 diabetes. The associations were all significant when using three different markers for HbA1c variability. To the best of our knowledge, there are no standardized definitions for HbA1c variability, and our findings suggest that SD and CV could both predict cardiovascular risk in patients with type 2 diabetes.

In subgroup analyses, several significant interactions were observed. HRs of cardiovascular disease associated with different visit-to-visit HbA1c variability markers were more pronounced in patients with comparatively lower BMI and lower mean HbA1c levels. These findings could be clinically important. Patients with lower mean HbA1c levels and large HbA1c variability appear to be more probable to have hypoglycaemia than those with continuously higher mean HbA1c levels. However, HbA1c variability was not significantly associated with cardiovascular disease in current and past smokers, as well as those who did not use lipid- or blood pressure-lowering medications. No significant associations were observed in patients who were using α-glucosidase inhibitors, GLP-1 receptor agonists, meglitinides, thiazolidinediones and SGLT2 inhibitors. This might be because of the limited sample size of cases detected, resulting in insufficient statistical power.

The underlying mechanism for the relationship between large HbA1c variability and cardiovascular disease in patients with type 2 diabetes is unclear. A recent UK study[21] identified the greatest elevation of visit-to-visit glycaemic variability in young and insulin-resistant men. Large glycaemic variability has also been associated with poor adherence to treatment, poor self-efficacy in diabetes management, complications with co-morbid conditions and poor quality of life with a lack of support.[22] We did not investigate the confounding factors associated with HbA1c variability because of a lack of sociodemographic variables in the electronic medical record data. However, a triangular association between HbA1c variability, severe hypoglycaemic events and incident cardiovascular disease was investigated. Large visit-to-visit HbA1c variability may be associated with a high risk of cardiovascular disease through an increased risk of severe hypoglycaemic events. Future investigation into other factors influencing visit-to-visit HbA1c variability will be of great interest. Damage can persist in cells exposed to high glucose levels long after the return of normoglycaemia, a concept known as cellular metabolic memory.[23] High glucose levels also cause irreversible epigenetic modifications, resulting in β-cell dysfunction and insulin resistance.[24] Thus, adverse cardiovascular outcomes may result from a combination of these risk factors.

Inevitably, the study has several limitations. First, some information, including duration of diabetes, education level and family income, were unavailable in the electronic data, which may be important to our study topic. Our findings were applicable to a 4-year follow-up period, but further studies with a longer follow-up are required for validation. Second, the cardiovascular diagnosis in the present study was based on a physician's diagnosis and no chart review was performed. However, most American and European cohort studies, such as the Framingham Study,[25] the Kaiser Permanente Medical Care Program[26] and the Atherosclerosis Risk in Communities Study,[27] used the same method to diagnose cardiovascular events. In addition, our analyses adjusted for some confounding factors, but unmeasured factors such as family history of diabetes, other related chronic diseases, dietary factors and physical activity could not be evaluated. Finally, the data used in this analysis were from healthcare systems located in south Louisiana, and some sociodemographic characteristics of these patients may differ from those in other geographic areas of the United States and elsewhere, limiting the generalizability of our findings. Exposure misclassification is a possibility in this study because the prescription data represented dispensations and not actual consumption.

In conclusion, the present analysis using data from large healthcare systems found a positive association between visit-to-visit HbA1c variability and incident cardiovascular disease in patients with type 2 diabetes, irrespective of the definition of HbA1c variability. Further analysis showed a mediating effect of severe hypoglycaemia in the association between visit-to-visit HbA1c variability and incident cardiovascular disease. Our findings suggest that HbA1c variability over a specific time period could be considered a supplementary glycaemic target, and therapies that can reduce large HbA1c variability as well as associated severe hypoglycaemic events are recommended for patients with type 2 diabetes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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TABLE 1

Baseline characteristics of the study population

	HbA1c SD				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for trend**
Participants (n)	6768	7406	7517	7569	
Age (y)	68.6 ± 11.3	68.1 ± 11.4	65.9 ± 11.4	66.0 ± 11.6	<.001
Male (%)	38.5	43.5	48.6	52.3	<.001
Race (%)					<.001
African American	40.1	38.4	36.3	47.3	
White	59.9	61.6	63.7	52.7	
Body mass index (kg/m^2)	32.7 ± 7.38	33.0 ± 7.23	33.6 ± 7.38	34.0 ± 7.45	<.001
Blood pressure (mmHg)					
Systolic	132 ± 11	133 ± 11	133 ± 11	134 ± 12	<.001
Diastolic	75 ± 7	75 ± 7	75 ± 7	77 ± 7	<.001
Mean HbA1c(%)	6.3 ± 0.7	6.7 ± 0.8	7.5 ± 1.1	8.6 ± 1.5	<.001
Total cholesterol (mg/dL)	172 ± 33.9	168 ± 33.9	167 ± 34.6	175 ± 38.6	<.001
Low-density lipoprotein cholesterol (mg/dL)	99.6 ± 28.2	95.9 ± 28.2	94.5 ± 28.4	101 ± 31.5	.008
High-density lipoprotein cholesterol (mg/dL)	47.8 ± 12.1	45.8 ± 11.8	43.1 ± 11.3	42.3 ± 11.2	<.001
Triglycerides (mg/dL)	127 ± 66.0	136 ± 68.1	152 ± 87.3	167 ± 113	<.001
Non-high-density lipoprotein cholesterol to high-density lipoprotein cholesterol ratio	2.77 ± 1.02	2.85 ± 1.07	3.07 ± 1.19	3.35 ± 1.29	<.001
Estimated GFR (mL/min/1.73m^2) (%)					.188
≥90	13.7	13.5	15.0	18.5	
60–89	63.7	61.0	58.3	55.3	
30–59	20.7	22.8	23.2	22.5	
15–29	1.4	1.8	2.2	2.5	
<15	0.5	0.9	1.3	1.3	
Body mass index categories (%)					<.001
<25 kg/m^2	11.6	10.1	8.6	8.2	
25–29.9 kg/m^2	28.8	28.0	25.4	23.4	
30.0–34.9 kg/m^2	28.3	29.3	29.0	28.6	
≥35 kg/m^2	31.2	32.6	37.0	39.8	

	HbA1c SD				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for trend**
Current smoker (%)	18.4	20.1	20.0	21.2	<.001
Insurance type (%)					<.001
Commercial/private	37.2	38.9	43.9	53.8	
Medicare	58.6	57.1	51.5	39.5	
Medicaid	2.3	2.1	2.7	4.2	
Self-pay	1.0	0.7	0.9	1.1	
Others	0.9	1.2	1.0	1.4	
Use of medications (%)					
Lipid-lowering	65.7	68.1	69.1	67.0	.061
Statin	63.5	65.9	66.8	64.8	
Fibrate	1.3	1.6	1.8	1.7	
Niacin	0.3	0.4	0.6	0.4	
Bile acid sequestrant	0.3	0.7	0.9	0.8	
PCSK9 inhibitor	0.9	1.1	1.3	1.6	
Others	0.2	0.2	0.3	0.3	
Antihypertensive	78.3	81.5	82.7	82.1	<.001
β-blocker	35.3	38.9	40.4	37.4	
Calcium channel blocker	36.4	39.3	38.5	37.0	
ACE inhibitor	43.1	47.2	50.9	53.7	
ARB	29.1	31.4	30.0	28.1	
α-blocker	11.4	12.3	12.5	13.7	
Diuretic	49.4	51.9	51.6	49.9	
Clonidine	1.2	1.4	1.5	1.8	
Glucose-lowering	65.0	79.1	90.4	93.9	<.001
Metformin	56.2	64.6	70.3	72.4	<.001
Insulin	6.2	17.5	39.3	58.8	<.001
Sulphonylurea	12.0	28.3	44.2	46.2	<.001
DPP4 inhibitors	6.1	15.0	26.6	27.5	<.001
α-glucosidase inhibitors	0.3	0.7	1.1	1.1	<.001
GLP-1 receptor agonists	2.9	6.5	15.8	20.1	<.001

	HbA1c SD				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P* for trend**
Meglitinides	0.5	1.1	2.3	2.4	<.001
Thiazolidinediones	2.0	3.6	6.2	6.1	<.001
SGLT2 inhibitors	1.5	5.1	12.9	15.6	<.001
Antiplatelet or anticoagulant	12.2	14.1	15.5	17.4	<.001

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; DPP4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; PCSK9, proprotein convertase subtilisin/kexin type 9; SGLT2, sodium-glucose co-transporter-2.

TABLE 2

Hazard ratios for risk of cardiovascular disease according to visit-to-visit HbA1c variability

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend	Per 1-unit increase[a]
HbA1c SD						
No. of patients	6768	7406	7517	7569		
No. of cases	673	1018	1064	991		
Person-years	27 900	31 363	32 044	30 964		
Age, sex and race, adjusted HR (95% CI)	1.00	1.36 (1.24–1.50)	1.53 (1.39–1.68)	1.78(1.61–1.97)	<.001	1.30 (1.24–1.37)
Model 1, HR (95% CI)[b]	1.00	1.31 (1.20–1.45)	1.42 (1.30–1.59)	1.62 (1.45–1.80)	<.001	1.22 (1.14–1.28)
Model 2, HR (95% CI)[c]	1.00	1.30 (1.18–1.42)	1.40 (1.26–1.55)	1.59 (1.41–1.77)	<.001	1.18(1.08–1.27)
HbA1c CV						
No. of patients	6851	7388	7488	7533		
No. of cases	656	999	1083	1008		
Person-years	28 312	31 429	31 860	30 669		
Age, sex and race, adjusted HR (95% CI)	1.00	1.39 (1.26–1.54)	1.63 (1.48–1.80)	1.87 (1.70–2.07)	<.001	1.28 (1.22–1.34)
Model 1, HR (95% CI)[b]	1.00	1.33 (1.20–1.48)	1.51 (1.36–1.68)	1.70 (1.53–1.90)	<.001	1.17(1.10–1.23)
Model 2, HR (95% CI)[c]	1.00	1.32 (1.18–1.47)	1.55 (1.39–1.73)	1.74 (1.53–1.97)	<.001	1.20(1.15–1.26)
Adjusted HbA1c SD						
No. of patients	6641	7414	7560	7645		
No. of cases	638	1019	1064	1025		
Person-years	27 105	31 336	32 299	31 531		
Age, sex and race, adjusted HR (95% CI)	1.00	1.40 (1.27–1.54)	1.54 (1.40–1.70)	1.83 (1.65–2.03)	<.001	1.36 (1.28–1.43)
Model 1, HR (95% CI)[b]	1.00	1.32 (1.18–1.45)	1.45 (1.30–1.61)	1.66 (1.48–1.86)	<.001	1.21 (1.14–1.29)
Model 2, HR (95% CI)[c]	1.00	1.31 (1.17–1.45)	1.50 (1.35–1.68)	1.80 (1.58–2.04)	<.001	1.30 (1.20–1.40)

Abbreviations: CI, confidence interval; CV, coefficient of variation; SD, standard deviation.

[a]Per 10 unit increase for HbA1c CV.

[b]Model 1 adjusted for age, race, sex, smoking, body mass index, systolic blood pressure, non-HDL/HDL ratio, estimated glomerular filtration rate, insurance type, hypoglycaemia events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications and antiplatelet as well as anticoagulant medications by category differences.

[c]Model 2 adjusted for the covariates in model 1 plus the updated mean value of HbA1c.

TABLE 3

Hazard ratios for risk of coronary heart disease according to visit-to-visit HbA1c variability

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend	Per 1-unit increase[a]
HbA1c SD						
No. of patients	6768	7406	7517	7569		
No. of cases	399	651	672	626		
Person-years	24 108	27 633	28 357	27 019		
Age, sex and race, adjusted HR (95% CI)	1.00	1.39 (1.23–1.57)	1.46 (1.29–1.66)	1.71 (1.50–1.94)	<.001	1.30 (1.24–1.37)
Model 1, HR (95% CI)[b]	1.00	1.32 (1.16–1.50)	1.32(1.15–1.51)	1.52 (1.32–1.74)	<.001	1.16(1.08–1.25)
Model 2, HR (95% CI)[c]	1.00	1.31 (1.14–1.49)	1.40 (1.22–1.60)	1.71 (1.46–2.01)	<.001	1.27(1.15–1.37)
HbA1c CV						
No. of patients	6851	7388	7488	7533		
No. of cases	394	637	681	636		
Person-years	24 429	27 672	28 212	26 804		
Age, sex and race, adjusted HR (95% CI)	1.00	1.40 (1.23–1.59)	1.54 (1.36–1.74)	1.77(1.55–2.01)	<.001	1.27 (1.20–1.35)
Model 1, HR (95% CI)[b]	1.00	1.31 (1.15–1.50)	1.41 (1.23–1.60)	1.55 (1.35–1.79)	<.001	1.15 (1.08–1.22)
Model 2, HR (95% CI)[c]	1.00	1.30 (1.14–1.49)	1.46 (1.28–1.66)	1.65 (1.42–1.90)	<.001	1.20(1.12–1.29)
Adjusted HbA1c SD						
No. of patients	6641	7414	7560	7645		
No. of cases	375	656	667	650		
Person-years	23 366	27 597	28 589	27 566		
Age, sex and race, adjusted HR (95% CI)	1.00	1.45 (1.27–1.64)	1.48 (1.30–1.68)	1.77 (1.55–2.01)	<.001	1.32 (1.23–1.42)
Model 1, HR (95% CI)[b]	1.00	1.34 (1.17–1.54)	1.30(1.12–1.50)	1.58(1.36–1.81)	<.001	1.20 (1.10–1.30)
Model 2, HR (95% CI)[c]	1.00	1.40 (1.23–1.60)	1.42 (1.22–1.61)	1.71 (1.46–2.03)	<.001	1.32 (1.21–1.45)

Abbreviations: CI, confidence interval; CV, coefficient of variation; SD, standard deviation.

[a]Per 10 unit increase for HbA1c CV.

[b]Model 1 adjusted for age, race, sex, smoking, body mass index, systolic blood pressure, non-HDL/HDL ratio, estimated glomerular filtration rate, insurance type, hypoglycaemia events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications and antiplatelet and anticoagulant medications by category differences.

[c]Model 2 adjusted for covariates in model 1 plus the updated mean value of HbA1c.

TABLE 4

Hazard ratios for risk of stroke according to visit-to-visit HbA1c variability

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*P* for trend	Per 1-unit increase[a]
HbA1c SD						
No. of patients	6768	7406	7517	7569		
No. of cases	346	492	505	508		
Person-years	28 544	32 446	33 161	31 903		
Age, sex and race, adjusted HR (95% CI)	1.00	1.27(1.11–1.46)	1.42 (1.24–1.63)	1.86 (1.62–2.14)	<.001	1.37 (1.27–1.47)
Model 1, HR (95% CI)[b]	1.00	1.23 (1.07–1.43)	1.40(1.21–1.61)	1.76 (1.50–2.04)	<.001	1.29 (1.20–1.40)
Model 2, HR (95% CI)[c]	1.00	1.23 (1.05–1.41)	1.42 (1.22–1.65)	1.86 (1.55–2.22)	<.001	1.30 (1.17–1.43)
HbA1c CV						
No. of patients	6851	7388	7488	7533		
No. of cases	329	481	523	518		
Person-years	28 954	32 495	32 975	31 631		
Age, sex and race, adjusted HR (95% CI)	1.00	1.33 (1.15–1.52)	1.59 (1.38–1.82)	2.00 (1.74–2.30)	<.001	1.32 (1.24–1.41)
Model 1, HR (95% CI)[b]	1.00	1.30(1.13–1.50)	1.54 (1.33–1.79)	1.92 (1.65–2.23)	<.001	1.22 (1.14–1.30)
Model 2, HR (95% CI)[c]	1.00	1.30(1.12–1.50)	1.53 (1.30–1.77)	1.93 (1.62–2.26)	<0.001	1.20(1.11–1.30)
Adjusted HbA1c SD						
No. of patients	6641	7414	7560	7645		
No. of cases	331	484	515	521		
Person-years	27 711	32 428	33 399	32 517		
Age, sex and race, adjusted HR (95% CI)	1.00	1.26 (1.10–1.45)	1.45 (1.27–1.67)	1.87 (1.63–2.15)	<.001	1.43 (1.32–1.55)
Model 1, HR (95% CI)[b]	1.00	1.24 (1.06–1.42)	1.40 (1.20–1.62)	1.80 (1.54–2.09)	<.001	1.33 (1.22–1.44)
Model 2, HR (95% CI)[c]	1.00	1.26 (1.09–1.45)	1.42 (1.21–1.66)	1.90 (1.59–2.28)	<.001	1.40 (1.26–1.55)

Abbreviations: CI, confidence interval; CV, coefficient of variation; HR, hazard ratio; SD, standard deviation.

[a]Per 10 unit increase for HbA1c CV.

[b]Model 1 adjusted for age, race, sex, smoking, body mass index, systolic blood pressure, non-HDL/HDL ratio, estimated glomerular filtration rate, insurance type, hypoglycaemia events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications and antiplatelet and anticoagulant medications by category differences.

[c]Model 2 adjusted for covariates in model 1 plus the updated mean value of HbA1c.

TABLE 5

Hazard ratios for risk of cardiovascular disease according to visit-to-visit HbA1c variability as a continuous measure in different subgroups

	HbA1c SD	HbA1c CV[a]	Adjusted HbA1c SD
Age, y			
<65	1.15 (1.04–1.28)	1.10 (1.02–1.20)	1.21 (1.08–1.34)
≥65	1.30 (1.20–1.42)	1.19 (1.12–1.27)	1.36 (1.25–1.50)
Sex			
Male	1.16(1.05–1.27)	1.12 (1.01–1.20)	1.20 (1.07–1.33)
Female	1.34 (1.21–1.48)	1.26(1.17–1.35)	1.40 (1.26–1.55)
Race			
African-American	1.20 (1.09–1.32)	1.15 (1.06–1.24)	1.23 (1.11–1.33)
White	1.30 (1.18–1.45)	1.23 (1.14–1.33)	1.34 (1.20–1.50)
Baseline body mass index[b]			
<30 kg/m^2	1.32 (1.18–1.47)	1.24 (1.14–1.34)	1.40 (1.26–1.57)
≥30 kg/m^2	1.18 (1.08–1.30)	1.15 (1.07–1.22)	1.25 (1.13–1.37)
Mean HbA1c level[b]			
<7.0%	1.54 (1.30–1.76)	1.32 (1.24–1.50)	1.60 (1.35–1.84)
≥7.0%	1.15 (1.08–1.25)	1.13 (1.06–1.22)	1.20(1.11–1.30)
Smoking status[b]			
Current and past smoking	1.07 (0.92–1.21)	1.01 (0.92–1.14)	1.10 (0.92–1.23)
Never smoking	1.34 (1.21–1.42)	1.24 (1.16–1.32)	1.40 (1.30–1.54)
Glucose-lowering medications			
No use	1.40 (1.07–1.82)	1.26 (1.05–1.55)	1.46 (1.08–1.95)
Metformin	1.21 (1.13–1.30)	1.19 (1.12–1.27)	1.25 (1.16–1.35)
Insulin	1.19 (1.09–1.29)	1.14 (1.06–1.22)	1.23 (1.13–1.35)
Sulphonylurea	1.11(1.01–1.21)	1.12 (1.03–1.22)	1.14 (1.03–1.25)
DPP4 inhibitors	1.29 (1.14–1.46)	1.27 (1.13–1.42)	1.34(1.17–1.52)
α-glucosidase inhibitors[b]	0.89 (0.461.70)	0.98 (0.54–1.78)	0.90 (0.45–1.78)
GLP-1 receptor agonists[b]	1.16 (0.98–1.37)	1.20 (1.03–1.40)	1.18(0.99–1.41)

	HbA1c SD	HbA1c CV[a]	Adjusted HbA1c SD
Meglitinides[b]	0.98 (0.66–1.45)	1.05 (0.73–1.49)	0.99 (0.66–1.50)
Thiazolidinediones[b]	1.16 (0.86–1.56)	1.13 (0.86–1.50)	1.19 (0.87–1.63)
SGLT2 inhibitors[b]	1.20 (0.97–1.50)	1.21 (0.99–1.48)	1.24 (0.98–1.56)
Lipid-lowering medications[b]			
No use	1.11 (0.95–1.26)	1.07 (0.93–1.17)	1.13 (0.96–1.32)
Use	1.31 (1.21–1.42)	1.23 (1.15–1.30)	1.38 (1.25–1.48)
Antihypertensive medications[b]			
No use	1.14 (0.91–1.43)	1.06 (0.86–1.23)	1.15 (0.90–1.46)
β-blocker	1.20(1.12–1.29)	1.24 (1.15–1.34)	1.21 (1.14–1.29)
Calcium channel blocker	1.20(1.11–1.29)	1.23 (1.14–1.34)	1.19 (1.12–1.27)
ACE inhibitor	1.16 (1.07–1.24)	1.19 (1.10–1.29)	1.16 (1.09–1.24)
ARB	1.27 (1.16–1.40)	1.32 (1.20–1.46)	1.26(1.16–1.36)
α-blocker	1.13 (1.03–1.22)	1.16(1.07–1.25)	1.20(1.10–1.31)
Diuretic	1.27(1.18–1.36)	1.31 (1.22–1.41)	1.26 (1.18–1.34)

Note: Adjusted for age, race, sex, smoking, body mass index, systolic blood pressure, non-high-density lipoprotein/high-density lipoprotein ratio, estimated glomerular filtration rate, insurance type, hypoglycaemia events, glucose-lowering medications, antihypertensive medications, lipid-lowering medications and antiplatelet as well as anticoagulant medications by category differences plus the updated mean value of HbA1c.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; CV, coefficient of variation; DPP4, dipeptidyl peptidase-4; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; SD, standard deviation; SGLT2, sodium-glucose co-transporter-2.

[a]Per 10 unit increase for HbA1c CV.

[b]*P* for interaction <.05.