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ORIGINAL RESEARCH

Long-Term Visit-to-Visit Glycemic Variability as a Predictor of Major Adverse Limb and Cardiovascular Events in Patients With Diabetes

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BACKGROUND: Peripheral arterial disease (PAD) is a severe complication in patients with type 2 diabetes. Glycemic variability (GV) is associated with increased risks of developing microvascular and macrovascular diseases. However, few studies have focused on the association between GV and PAD.

METHODS AND RESULTS: This cohort study used a database maintained by the National Taiwan University Hospital, a tertiary medical center in Taiwan. For each individual, GV parameters were calculated, including fasting glucose coefficient of variability (FGCV) and hemoglobin A1c variability score (HVS). Multivariate Cox regression models were constructed to estimate the relationships between GV parameters and composite scores for major adverse limb events (MALEs) and major adverse cardiovascular events (MACEs). Between 2014 and 2019, a total of 45 436 adult patients with prevalent type 2 diabetes were enrolled for analysis, and GV was assessed during a median follow-up of 64.4 months. The average number of visits and time periods were 13.38 and 157.87 days for the HVS group and 14.27 and 146.59 days for the FGCV group, respectively. The incidence rates for cardiac mortality, PAD, and critical limb ischemia (CLI) were 5.38, 20.11, and 2.41 per 1000 person-years in the FGCV group and 5.35, 20.32, and 2.50 per 1000 person-years in HVS group, respectively. In the Cox regression model with full adjustment, the highest FGCV quartile was associated with significantly increased risks of MALEs (hazard ratio [HR], 1.57 [95% CI, 1.40–1.76]; $P<0.001$) and MACEs (HR, 1.40 [95% CI, 1.25–1.56]; $P<0.001$). Similarly, the highest HVS quartile was associated with significantly increased risks of MALEs (HR, 1.44 [95% CI, 1.28–1.62]; $P<0.001$) and MACEs (HR, 1.28 [95% CI, 1.14–1.43]; $P<0.001$). The highest FGCV and HVS quartiles were both associated with the development of PAD and CLI (FGCV: PAD [HR, 1.57; $P<0.001$], CLI [HR, 2.19; $P<0.001$]; HVS: PAD [HR, 1.44; $P<0.001$], CLI [HR, 1.67; $P=0.003$]). The Kaplan-Meier analysis showed significantly higher risks of MALEs and MACEs with increasing GV magnitude (log-rank $P<0.001$).

CONCLUSIONS: Among individuals with diabetes, increased GV is independently associated with the development of MALEs, including PAD and CLI, and MACEs. The benefit of maintaining stable glycemic levels for improving clinical outcomes warrants further studies.

Key Words: diabetes ■ glycemic variability ■ major adverse cardiovascular events ■ major adverse limb events ■ peripheral arterial disease

Type 2 diabetes (T2D) is a chronic metabolic disorder characterized by insulin resistance resulting from both environmental and genetic components and is one of the fastest-growing diseases worldwide, posing a major threat to global health. Globally, 451 million people were estimated to have diabetes in

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CLINICAL PERSPECTIVE

What Is New?

- Both fasting glucose coefficient of variability and glycated hemoglobin variability score with increased glycemic variability are independently associated with the development of peripheral arterial disease and critical limb ischemia.

What Are the Clinical Implications?

- In patients with type 2 diabetes, maintaining a stable glycemic variability may reduce the incidence of clinical outcomes, including major adverse limb events and major adverse cardiovascular events.

Nonstandard Abbreviations and Acronyms

CLI	critical limb ischemia
DPP4	dipeptidyl peptidase 4
FGCV	fasting glucose coefficient of variability
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
GV	glycemic variability
HVS	hemoglobin A1c variability score
MACE	major adverse cardiovascular event
MALE	major adverse limb event
SGLT2	sodium-glucose co-transporter-2
T2D	type 2 diabetes

2017, a population that is expected to reach 693 million by 2045.[1,2] Consistent hyperglycemia can lead to cardiovascular disease, which is the leading cause of death among patients with diabetes, including coronary artery disease, heart failure, ischemic stroke, and peripheral arterial disease (PAD).[3]

Diabetes has a pervasive influence on the atherothrombotic milieu of the peripheral vasculature, and PAD is a major manifestation of generalized atherosclerosis. Proatherogenic changes include increased inflammation and alterations in blood cell characteristics and hemostatic factors.[4] Patients with T2D with PAD are associated with a greater risk of amputation, and the presence of PAD is a marker of excess cardiovascular risk. A previous study showed that patients with major PAD presented with increased rates of all-cause mortality and major macrovascular events.[5]

Convincing evidence suggests that hyperglycemia has a detrimental effect on cardiovascular risk profiles, and intensive hyperglycemic control may reduce major macrovascular event occurrence; however, the increased risks of hypoglycemia and its associated consequences may compromise therapeutic approaches.[6,7] Glycemic fluctuations and chronic hyperglycemia can trigger inflammatory responses via increased endoplasmic reticulum stress and mitochondrial superoxide production, promoting the pathogenesis of endothelial dysfunction and atherogenesis.[8] Glycemic variability (GV) has adverse effects on autonomic function and increases the thrombotic properties of platelets, leading to the development of macrovascular disease.[9,10] In addition, GV was found to be an independent risk factor for diabetic peripheral neuropathy, one of the most common microvascular complications experienced by patients with diabetes.[11] However, few studies have focused on the association between GV and PAD, particularly the effects on major limb events. Plasma fasting glucose coefficient of variability (FGCV) and hemoglobin A1c (HbA1c) levels were found to be associated with new-onset PAD in Taiwan, but HbA1c variability has not been studied. A recent study reported that GV in patients without diabetes was found to increase the incidence of PAD in Korea.[12–14]

The present study investigated the association between GV and the occurrence of major adverse limb events (MALEs), including PAD and critical limb ischemia (CLI), in patients with diabetes. We also examined the impacts of GV on major adverse cardiovascular events (MACEs), including cardiovascular mortality, myocardial infarction, and stroke.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Data Collection

This study obtained detailed medical information from the National Taiwan University Hospital-Integrated Medical Database. We enrolled patients >50 years of age who were diagnosed with T2D (either prevalent or incident cases) at the National Taiwan University Hospital from January 1, 2014 to December 31, 2019. The index date for this cohort study was defined as the date of T2D diagnosis and established according to *International Classification of Diseases* (*ICD*) codes (ICD9: 250.XX, ICD10: E08.XX, E11.XX). Patients with any previous history of acute myocardial infarction (AMI), ischemic stroke, or lower-extremity arterial disease, including PAD or CLI, were excluded from this study. Patients were followed from the index date (ie, the date of T2D diagnosis) until the occurrence of any study outcome, death, or December 31, 2019, whichever came first. The study protocol was approved by the institutional review board of National Taiwan

University Hospital, and informed consent was waived because of the use of deidentified patient data.

Baseline characteristics, including body mass index and diagnoses of hypertension, hyperlipidemia, and coronary artery disease (CAD), were obtained from electronic health records. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. Prescription medications were categorized into β-blockers; calcium channel blockers; angiotensin-converting enzyme inhibitors; angiotensin receptor blockers; diuretics; statins; anticoagulants, including direct oral anticoagulants and warfarin; and antidiabetic medications, including insulin, metformin, SGLT2 (sodium-glucose co-transporter-2) inhibitor, DPP4 (dipeptidyl peptidase 4) inhibitor, sulfonylurea, repaglinide, acarbose, thiazolidinedione, and GLP-1 (glucagon-like peptide-1) agonist.

The outcomes were the incidence of MALEs, defined as the first event of newly diagnosed PAD or newly diagnosed CLI, and the incidence of MACEs, defined as cardiovascular mortality, nonfatal myocardial infarction, or nonfatal ischemic stroke. Death events were evaluated by a central committee, and cardiac mortality was determined according to information in the electronic health records. The index dates for all outcomes were defined as the date of initial diagnosis. All medical records were reviewed until the last clinical visit or death.

Glycemic Variability Measurement

For each individual, fasting plasma glucose (FPG) and HbA1c levels were measured quarterly at the outpatient department, and mean values of FGCV and the HbA1c variability score (HVS) were calculated. FPG was measured in subjects who reported fasting at least 8 hours before testing. Missing values were discarded. The SD of FPG values was divided by the mean FPG value, which was further divided by the square root of the ratio of FPG measurements n to n–1 ($\sqrt{n/(n-1)}$) to obtain FGCV (%). The HVS was calculated as the number of measurements for each individual in which HbA1c changed by >0.5% (5.5 mmol/mol) from the prior value, expressed as a percentage of the total number of HbA1c measurements.[15]

Statistical Analysis

Patients were categorized according to FGCV and HVS quartiles. Continuous variables are described as the mean (SD), and categorical variables are expressed as the frequency (percentage). Differences among groups were tested by the χ^2 test for categorical variables and by 1-way ANOVA for continuous variables. Multivariate Cox proportional hazards models were constructed to evaluate the association of GV with other variables, and the results are presented as hazard ratios (HRs) and 95% CIs. The Cox regression models were sequentially adjusted for covariates. Model 1 was a crude model without adjustment. Model 2 was adjusted for age, sex (men were used as the reference group), baseline body mass index, history of hypertension, history of CAD, baseline FPG, baseline HbA1c, and baseline eGFR. Model 3 was adjusted as described for Model 2 plus the use of antidiabetic medications, including metformin, SGLT2 inhibitor, DDP4 inhibitor, and GLP-1 agonist.

Because most subjects were regularly followed up every 3 months in our T2D cohort, we assumed that censoring was noninformative censoring, and therefore the distribution of survival time provides no information about the distribution of censorship times and vice versa. When conducting Cox regression analyses, proportional hazard was assumed, and censoring was indicated and treated as right censoring. The proportional hazard assumption was examined by using the goodness-of-fit test and was focused on the primary interested variable, HVS. The result of goodness-of-fit showed that the proportional hazard assumption was held for HVS (P>0.05, data not shown).

Survival analyses were performed using the Kaplan-Meier method, and significant differences were determined by the log-rank test. Pairwise comparisons were conducted when significant differences were identified in the overall comparison using the log-rank test. Further subgroup analyses were conducted according to age (dichotomized at 65 years), sex, body mass index (dichotomized at 25 kg/m^2), baseline FPG (dichotomized at 200 mg/dL), baseline eGFR (dichotomized at 60 mL/min per 1.73 m^2), history of hypertension, history of CAD, metformin use, SGLT2 inhibitor use, DPP4 inhibitor use, and GLP-1 agonist use.

All statistical analyses were performed using SAS statistical software (version 9.4.; SAS Institute, Cary, NC) and R (version 4.1.2; R Foundation for Statistical Computing). A 2-tailed P value of <0.05 was considered significant.

RESULTS

Baseline Characteristics

A flowchart illustrating the patient selection process is shown in Figure 1. A total of 74 835 patients with diagnosed T2D were identified between 2014 and 2019. Among them, 121 patients without firm evidence of T2D (lacking blood tests or evidence of antidiabetic medication use) and 1607 patients <50 years of age were excluded. We excluded 176 patients with a prior history of acute myocardial infarction, 755 patients with a prior history of ischemic stroke, 1247 patients with a prior history of PAD, and 35 patients with a

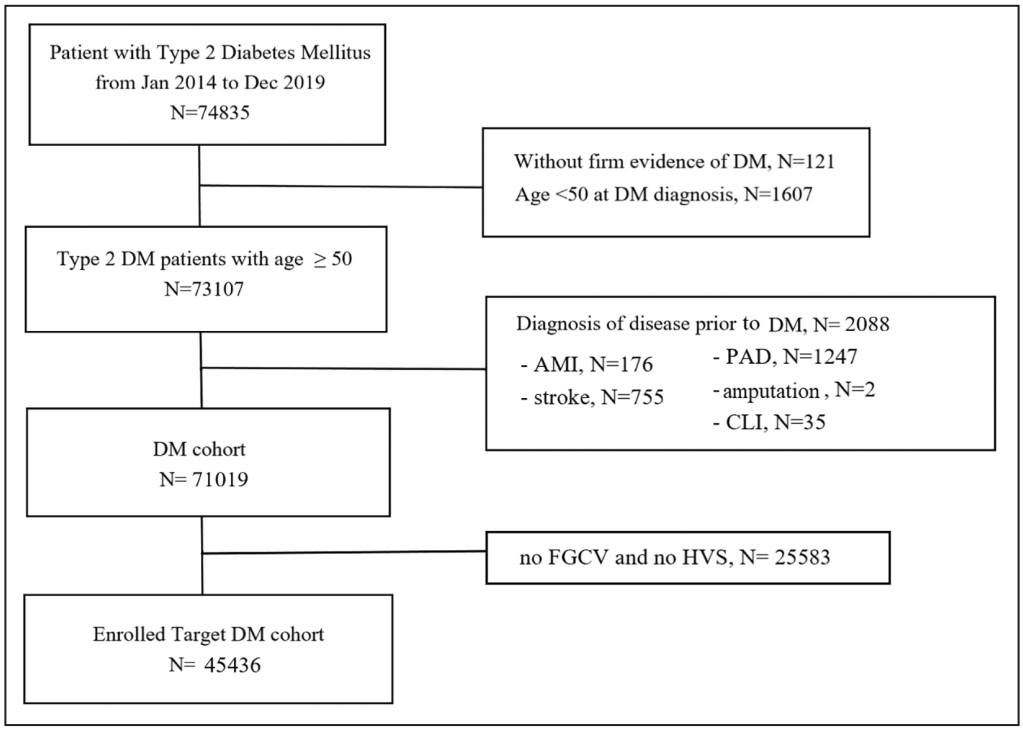

Figure 1. Flowchart of patient selection procedures.
AMI indicates acute myocardial infarction; CLI, critical limb ischemia; DM, diabetes mellitus; FGCV, fasting glucose coefficient of variability; HVS, hemoglobin A1c variability score; and PAD, peripheral arterial disease.

prior history of CLI. We also excluded 25 583 patients with missing FGCV and HVS values. Finally, a total of 45 436 subjects were evaluated in the final analysis. A majority (>80%) of patients had GV. The patients were grouped according to FGCV or HVS quartiles, and their baseline characteristics according to quartiles are displayed in Table 1 and Table S1. The cut-off values used to define the 4 FGCV quartiles were 9.01%, 14.61%, 23.70%, and the thresholds defined for the 4 HVS quartiles were 0.01%, 22.01%, 48.41%. The subjects in the highest FGCV quartile were older, more likely to be men, had higher baseline FPG and HbA1c levels, had worse baseline eGFR levels, were more likely to have new onset of PAD, and were less likely to have hypertension or CAD than patients in the other quartiles. The subjects in the highest HVS quartile were more likely to be men, were less likely to have hypertension, and had higher baseline FPG and HbA1c levels than patients in the other quartiles. In addition, the baseline characteristics of patients with available HbA1c/fasting glucose data to calculate variability and those without available data are provided in Table S2. Compared with those included in the analytical cohort, the patients with missing HbA1c and/or fasting glucose values had fewer comorbidities and less antidiabetic medication prescribed. We have also analyzed the correlation between FGCV and HVS with the Pearson correlation test (Figure S1) (r=0.39, P<0.001).

The distribution of number of fasting glucose and HbA1c measurements was provided in Table S3. Over a median follow-up period of 64.5 months, adverse events reported in the FGCV groups (N=43 206) included 1001 cardiac mortalities (overall incidence rate of 33.02 per 1000 person-years), 3521 PAD events (overall incidence rate of 20.11 per 1000 person-years), and 446 CLI events (overall incidence rate of 2.41 per 1000 person-years). In the HVS groups (N=42 011), 981 cardiac mortalities (overall incidence rate of 20.32 per 1000 person-years), 3502 PAD events (overall incidence rate of 20.32 per 1000 person-years), and 456 CLI events (overall incidence rate of 2.50 per 1000 person-years) were reported.

The incidence rates of PAD in each FGCV quartile, from low to high, were 14.04, 14.67, 20.25, and 32.54 per 1000 person-years. The incidence rates of PAD in each HVS quartile, from low to high, were 15.47, 15.30, 21.64, and 30.75 per 1000 person-years. The incidence rates of CLI in each FGCV quartile, from low to high, were 0.99, 0.99, 2.12, and 5.71 per 1000 person-years. The incidence rates of CLI in each HVS quartile, from low to high, were 1.49, 0.92, 2.70, and 5.30 per 1000 person-years. The incidence rates of cardiac mortality in each FGCV quartile, from low to high, were

Table 1. Baseline Patients' Characteristics

	HVS				
	Q1, 0%	Q2, 0.01%–22.00%	Q3, 22.01%–48.40%	Q4, 48.41%–99.00%	*P* value
N (%)	10364 (23.99)	10495 (24.29)	10839 (25.09)	10313 (23.87)	
Age, y	67.92 (9.92)	66.89 (9.37)	67.04 (9.88)	67.43 (10.20)	<0.001
Men	5160 (49.79)	5368 (51.15)	5730 (52.86)	5717 (55.43)	<0.001
Baseline BMI, kg/m^2 (%)	25.21 (4.07)	25.68 (4.17)	25.78 (4.41)	25.51 (4.43)	<0.001
Hypertension	2285 (22.05)	2160 (20.58)	1678 (15.48)	1371 (13.29)	<0.001
CAD	1031 (9.95)	832 (7.93)	779 (7.19)	706 (6.85)	<0.001
Baseline FPG, mg/dL	117.61 (32.21)	128.79 (33.30)	143.23 (49.36)	156.93 (64.98)	<0.001
Baseline HbA1c, (%)	6.34 (0.74)	6.87 (0.99)	7.48 (1.38)	8.05 (1.78)	<0.001
Baseline eGFR, mL/min per 1.73 m^2	69.00 (27.64)	71.68 (27.64)	68.77 (30.22)	65.74 (32.52)	<0.001
Medication					
Antiplatelet	3631 (35.03)	4229 (40.30)	4785 (44.15)	4426 (42.92)	<0.001
Anticoagulant	646 (6.23)	664 (6.33)	746 (6.88)	743 (7.20)	0.014
CCB	4994 (48.19)	5789 (55.16)	6244 (57.61)	5741 (55.67)	<0.001
β-Blocker	3655 (35.27)	4085 (38.92)	4487 (41.40)	4077 (39.53)	<0.001
ACEI/ARB	5060 (48.82)	6538 (62.30)	6893 (63.59)	5899 (57.20)	<0.001
Diuretics	2426 (23.41)	2839 (27.05)	3803 (35.09)	3983 (38.62)	<0.001
Statin	4539 (43.80)	6238 (59.44)	6344 (58.53)	5014 (48.62)	<0.001
Insulin	1268 (12.23)	1787 (17.03)	3855 (35.57)	4955 (48.05)	<0.001
Metformin	4902 (47.30)	8522 (81.20)	8761 (80.83)	7283 (70.62)	<0.001
SGLT2 inhibitor	364 (3.51)	1379 (13.14)	2140 (19.74)	1571 (15.23)	<0.001
DPP4 inhibitor	2175 (20.99)	4891 (46.60)	6922 (63.86)	6300 (61.09)	<0.001
Sulphonylurea	1884 (18.18)	4830 (46.02)	6775 (62.51)	6077 (58.93)	<0.001
TZD	413 (3.98)	1468 (13.99)	2233 (20.60)	1869 (18.12)	<0.001
GLP-1 agonist	18 (0.17)	129 (1.23)	343 (3.16)	304 (2.95)	<0.001

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; FGCV, coefficients of variability of fasting glucose; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; HVS, hemoglobin A1c variability score; Q, quartile; SGLT2, sodium-glucose co-transporter-2; and TZD, thiazolidinediones.

4.04, 3.77, 4.79, and 9.13 per 1000 person-years. The incidence rates of cardiac mortality in each HVS quartile, from low to high, were 6.23, 2.51, 4.47, and 9.44 per 1000 person-years. A total of 6148 subjects experienced all-cause mortality in the FGCV groups, and 5846 subjects experienced all-cause mortality in the HVS groups.

Measures of GV and Outcomes

Compared with the lowest FGCV quartile, the highest FGCV quartile was significantly associated with a higher incidence of MALEs (HR, 1.57 [95% CI, 1.40–1.76]) in the fully adjusted Model 3 (Table S4). Among the individual MALE components, the highest FGCV quartile remained significantly associated with the incidence of PAD (HR, 1.57 [95% CI, 1.40–1.76]; *P*<0.001) and CLI (HR, 2.19 [95% CI, 1.51–3.17]; *P*<0.001). Using the first FGCV quartile as the reference quartile, the HRs for MACE development in Model 1 without covariate adjustments across the second to fourth quartiles, from low to high, were 1.13 (95% CI, 1.01–1.25; *P* = 0.026), 1.42 (95% CI, 1.29–1.57; *P*<0.001), and 2.12 (95% CI, 1.93–2.33; *P*<0.001). After adjustment for covariates, the fourth quartile remained significantly associated with MACE development, with HRs of 1.60 (95% CI, 1.44–1.79; *P*<0.001) for Model 2 and 1.40 (95% CI, 1.25–1.56; *P*<0.001) for the fully adjusted Model 3.

As shown in Table 2, using the first HVS quartile as the reference quartile, the fourth quartile remained significantly associated with a higher incidence of MALEs (HR, 1.44 [95% CI, 1.27–1.62]; *P*<0.001), PAD (HR, 1.23 [95% CI, 1.09–1.39]; *P*<0.001), and CLI (HR, 1.67 [95% CI, 1.18–2.35]; *P*=0.003), and the HR for MACE development remained significant for the fourth HVS quartile (HR, 1.28 [95% CI, 1.14–1.43]; *P*<0.001) in the fully adjusted Model 3. We performed restrictive cubic spline for nonlinear HR of MALEs and MACEs stratified by HVS. There were J-curve phenomenon of MACEs,

Table 2. Adjusted Hazard Ratios for MACE and MALE Across Quartiles of Glycemic Variability by HVS

Outcome	Group	No.	Event (%)	Model 1		Model 2		Model 3	
				HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Total mortality	HVS_Q1	10364	1370 (13.22)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	686 (6.54)	0.37 (0.34–0.41)	<0.001	0.43 (0.39–0.47)	<0.001	0.46 (0.41–0.51)	<0.001
	HVS_Q3	10839	1288 (11.88)	0.72 (0.67–0.77)	<0.001	0.75 (0.68–0.81)	<0.001	0.82 (0.75–0.90)	<0.001
	HVS_Q4	10313	2502 (24.26)	1.90 (1.78–2.03)	<0.001	1.84 (1.69–1.99)	<0.001	1.94 (1.78–2.11)	<0.001
MACE	HVS_Q1	10364	729 (7.03)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	752 (7.17)	0.87 (0.79–0.97)	0.008	0.88 (0.79–0.98)	0.019	0.79 (0.70–0.88)	<0.001
	HVS_Q3	10839	1112 (10.26)	1.30 (1.19–1.43)	<0.001	1.17 (1.05–1.30)	0.004	0.98 (0.87–1.09)	0.654
	HVS_Q4	10313	1282 (12.43)	1.85 (1.69–2.02)	<0.001	1.50 (1.35–1.67)	<0.001	1.28 (1.14–1.43)	<0.001
Cardiac mortality	HVS_Q1	10364	251 (2.42)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	132 (1.26)	0.39 (0.31–0.48)	<0.001	0.41 (0.33–0.52)	<0.001	0.42 (0.33–0.52)	<0.001
	HVS_Q3	10839	231 (2.13)	0.69 (0.58–0.83)	<0.001	0.59 (0.48–0.72)	<0.001	0.59 (0.48–0.73)	<0.001
	HVS_Q4	10313	367 (3.56)	1.53 (1.30–1.79)	<0.001	1.10 (0.90–1.34)	0.364	1.07 (0.87–1.32)	0.530
AMI	HVS_Q1	10364	202 (1.95)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	267 (2.54)	1.10 (0.92–1.32)	0.298	1.08 (0.89–1.32)	0.414	0.88 (0.72–1.08)	0.214
	HVS_Q3	10839	386 (3.56)	1.60 (1.35–1.90)	<0.001	1.36 (1.13–1.64)	0.001	0.97 (0.80–1.18)	0.775
	HVS_Q4	10313	465 (4.51)	2.39 (2.03–2.82)	<0.001	1.84 (1.52–2.23)	<0.001	1.39 (1.14–1.69)	0.001
Ischemic stroke	HVS_Q1	10872	337 (3.10)	Ref.		Ref.		Ref.	
	HVS_Q2	10970	398 (3.63)	1.12 (0.97–1.30)	0.123	1.05 (0.90–1.23)	0.515	0.98 (0.83–1.15)	0.777
	HVS_Q3	10711	470 (4.39)	1.35 (1.17–1.55)	<0.001	1.21 (1.04–1.41)	0.015	1.23 (1.05–1.44)	0.010
	HVS_Q4	10653	618 (5.80)	1.86 (1.63–2.13)	<0.001	1.52 (1.30–1.77)	<0.001	1.34 (1.14–1.58)	<0.001
MALE	HVS_Q1	10364	596 (5.75)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	764 (7.28)	1.09 (0.98–1.21)	0.113	1.04 (0.93–1.17)	0.499	1.02 (0.91–1.15)	0.707
	HVS_Q3	10839	1045 (9.64)	1.51 (1.36–1.67)	<0.001	1.31 (1.17–1.46)	<0.001	1.21 (1.08–1.36)	0.001
	HVS_Q4	10313	1100 (10.67)	1.94 (1.75–2.14)	<0.001	1.56 (1.39–1.76)	<0.001	1.44 (1.28–1.62)	<0.001
PAD	HVS_Q1	10364	596 (5.75)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	763 (7.27)	1.09 (0.98–1.21)	0.120	1.04 (0.93–1.16)	0.5120	1.02 (0.91–1.15)	0.730
	HVS_Q3	10839	1044 (9.63)	1.51 (1.36–1.66)	<0.001	1.31 (1.17–1.46)	<0.001	1.21 (1.08–1.36)	0.001
	HVS_Q4	10313	1099 (10.66)	1.94 (1.75–2.14)	<0.001	1.56 (1.39–1.75)	<0.001	1.44 (1.27–1.62)	<0.001
CLI	HVS_Q1	10364	60 (0.58)	Ref.		Ref.		Ref.	
	HVS_Q2	10495	48 (0.46)	0.62 (0.42–0.90)	0.013	0.60 (0.41–0.89)	0.0115	0.58 (0.39–0.87)	0.008
	HVS_Q3	10839	144 (1.33)	1.89 (1.40–2.55)	<0.001	1.30 (0.94–1.81)	0.1157	1.14 (0.81–1.61)	0.446
	HVS_Q4	10313	204 (1.98)	3.54 (2.66–4.72)	<0.001	1.93 (1.39–2.69)	<0.001	1.67 (1.18–2.35)	0.003

Model 1: not adjusted. Model 2: adjusted for age, sex, baseline body mass index, hypertension, coronary artery disease, average of fasting glucose, average HbA1c, baseline eGFR. Model 3: adjusted for model 2 plus medications (metformin, SGLT2 inhibitor, DDP4 inhibitor, GLP-1 agonist). AMI indicates acute myocardial infarction; CLI, critical limb ischemia; DPP4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, hemoglobin A1c; HVS, hemoglobin A1c variability score; MACE, major adverse cardiovascular event; MALE, major adverse limb events; PAD, peripheral arterial disease; Q, quartile; Ref., reference; and SGLT2, sodium-glucose co-transporter-2.

CLI, and cardiac mortality, as shown in Figure S2A through S2D. We also performed the analysis of HbA1c variability using SD and coefficient of variation (CV) in Tables S5 and S6.

The results of the Kaplan-Meier analysis are shown in Figure 2 and Figure S3, revealing that the probabilities of experiencing MALEs (Figure 2A and Figure S3A) and MACEs (Figure 2B and Figure S3B) were significantly different across FGCV and HVS quartiles (all log-rank $P<0.001$). Pairwise comparisons showed that the incidence of MACEs and MALEs differed significantly among quartiles, except for the first and second quartiles (Tables S7 and S8).

Subgroup Analyses of MALE and MACE Occurrence

Figure S4 illustrates the subgroup analyses for MALE and MACE occurrence in the FGCV groups using the first quartile as the reference quartile. The HRs for MACE and MALE occurrence in the fourth quartile remained significant in the fully adjusted Model 3 across different subgroup variables, except for baseline FPG

>200 mg/dL, HbA1c >8.5%, history of CAD, and SGLT2 inhibitor or GLP-1 agonist use. Similarly, we performed subgroup analyses for MACE and MALE occurrence in the HVS groups using the first quartile as the reference quartile (Figure 3). We found that the HRs in the fourth quartile remained significant across most subgroup variables, except for baseline FPG >200 mg/dL, HbA1c >8.5%, baseline eGFR ≤60 mL/min per 1.73 m^2, and history of CAD, SGLT2 inhibitor, DPP4 inhibitor, and GLP-1 agonist use. We further investigated the effects of GV on PAD and CLI among FGCV and HVS groups using subgroup analyses.

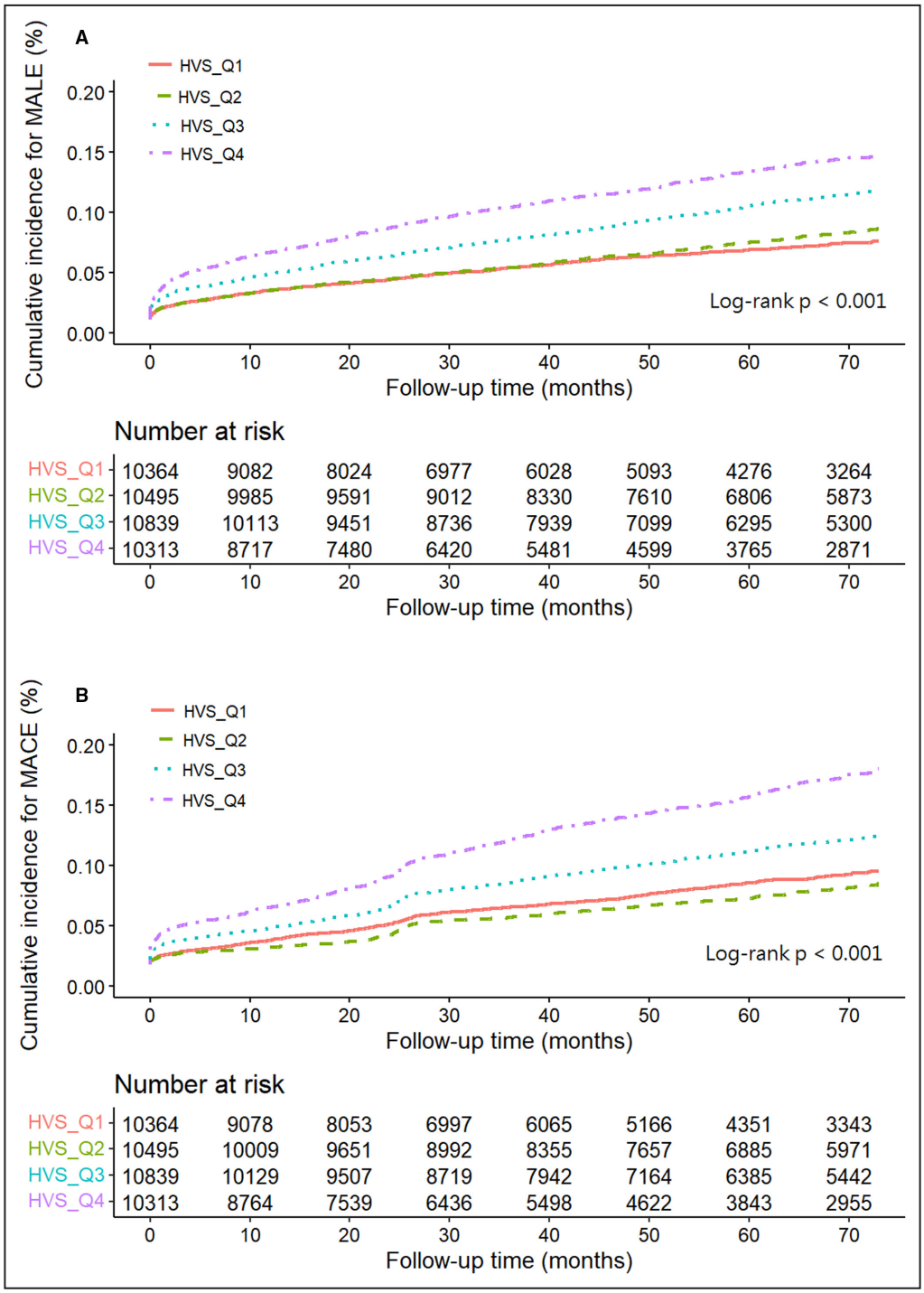

Figure 2. Cumulative event incidence for MALEs (A) and MACEs (B), stratified by HVS.
HVS indicates hemoglobin A1c variability score; MACE, major adverse cardiovascular event; and MALE, major adverse limb event.

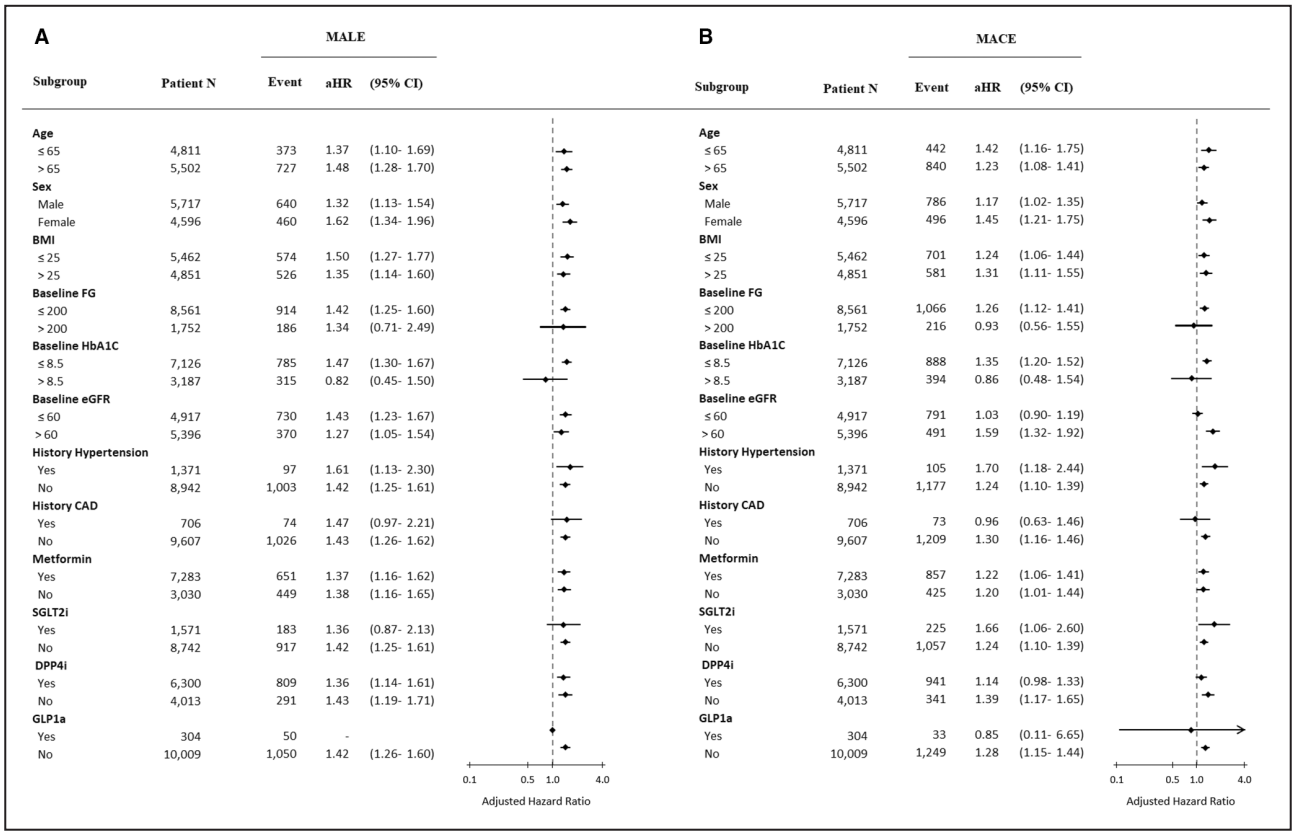

Figure 3. Subgroup analyses for MALEs (A) and MACEs (B) stratified by HVS.
BMI indicates body mass index; CAD, coronary artery disease; DPP4i, dipeptidyl peptidase 4 inhibitor; eGFR, estimated glomerular filtration rate; FG, fasting glucose; HbA1c, hemoglobin A1c; HR, hazard ratio; HVS, hemoglobin A1c variability score; GLP-1a, glucagon-like peptide-1 agonist; MACE, major adverse cardiac event; MALE, major adverse limb event; and SGLT2i, sodium-glucose co-transporter-2 inhibitor.

The risk in the fourth quartile was consistently higher regardless of subgroup variables, except for HbA1c >8.5% and GLP-1 agonist use (Figures S5 and S6).

DISCUSSION

In the current study, we first identified associations between GV and the incidences of MALEs and MACEs in a large cohort of patients with T2D. Our data demonstrated that higher GV is an independent predictor for both MALE and MACE incidence. Patients with T2D in the highest HVS quartile exhibited a 44% increase in MALE risk compared with the lowest HVS quartile after adjusting for confounding factors. In addition, patients with T2D in the highest FGCV quartile had a 57% increase in MALE risk compared with the lowest FGCV quartile. Increased FGCV and HVS were both associated with the development of PAD, CLI, MACEs, and total mortality, indicating that the association with GV was consistent regardless of whether FPG or HbA1c were used to assess GV.

T2D is an important risk factor for PAD, which is associated with cardiovascular complications and long-term disability in patients with T2D.[16,17] PAD is the primary cause of nontraumatic amputation, which is debilitating and portends poor prognosis. The 5-year survival rate is significantly lower for patients with T2D who undergo amputation because of the development of diabetic foot ulcers compared with patients who do not require amputation.[18,19] Early screening and interventions for modifiable risk factors associated with PAD development, such as smoking, hypertension, dyslipidemia, and obesity can reduce PAD risk and complications associated with PAD development.[20] In addition to traditional risk factors, recent evidence has suggested that GV may confer additional risk for the development of atherosclerosis, playing a crucial role in diabetes-related complications.[21] An observational study showed that decreased HbA1c levels and reduced HbA1c variability could improve ankle–brachial index values.[22]

Oxidative stress has been implicated in the underlying mechanism mediating the effects of GV, and evidence suggests that the stimulation of superoxide production together with NADPH oxidase increases the release of inflammatory cytokines, leading to endothelial dysfunction.[23–25] Both in vivo and in vitro studies have shown that fluctuations in glucose levels are associated with the increased production of reactive

oxygen species and enhanced vascular damage compared with chronic, persistent hyperglycemia.[26–28] High GV is also associated with the risk of hypoglycemia, which has been found to be an independent cause of cardiovascular damage through the release of inflammatory cytokines and increased platelet activation.[29,30] Collectively, high GV increases the risks associated with both hyperglycemia and hypoglycemia, subsequently inducing oxidative stress, inflammatory cytokine production, epigenetic changes, endothelial dysfunction, and β-cell dysfunction, more than sustained chronic hyperglycemia. Furthermore, higher GV was strongly associated with a larger plaque burden, ultimately contributing to diabetic complications and harmful consequences, including MACEs and MALEs.[31] These various detrimental pathways contribute to the increased incidence of both MALEs and MACEs associated with high GV.

The clinical relationship between GV and diabetic complications is difficult to ascertain because different studies use different methods to assess GV.[32] Short-term GV is typically measured within-day and between-day, whereas long-term GV is evaluated based on the serial assessment of HbA1c, serial FPG, or postprandial glucose measurements over longer periods of time. Previous studies have revealed that short-term GV is associated with increased plaque formation and poorer prognosis for acute coronary syndrome, whereas long-term GV has been independently associated with increased risks of MACE development and all-cause mortality.[33–35] Our data are in line with prior evidence that GV is adversely associated with MACE development, whereas no association between GV and MALE incidence has yet been reported.

Multiple metrics can be used to assess GV. Previous studies have shown that FGCV is an independent predictor of all-cause, cardiovascular, and cancer-related mortality.[36] In addition, GV (as assessed using the SDs and CVs for HbA1c and fasting glycemia) was found to be associated with both microvascular and macrovascular complications.[37,38] There were consistent results on the all-cause mortality and cardiovascular events when using different parameters on glycemic variability such as CV, SD, average successive variability, and variability independent of the mean.[35] Most studies evaluate HbA1c variability using the SD or CV for HbA1c values. Although both the SD and CV can reflect the distribution of HbA1c measures, these values can be difficult to interpret in clinical practice. Comparatively, HVS is more clinically tractable than either the SD or CV, and HVS has been established as an indicator of macrovascular and microvascular disease. In our study, we validated the use of HVS in the assessment of MALE risk, including PAD and CLI. HVS is advantageous because it is both significantly informative and clinically useful without incurring any major loss of information compared with the SD or CV of Hb1Ac values.

In the subgroup analysis, it is surprising and interesting that the impact of GV was greater in those with lower baseline glucose level (fasting glucose level <200 mg/dL and HbA1c <8.5%). In the previous study, Lee et al has reported this similar finding that the impact of GV was greater in those with fasting glucose level <126 mg/dL.[31] Patients with higher GV may have a shorter duration of diabetes, fewer comorbidities, and not be treated with antidiabetic medication so that they were more vulnerable to adverse outcomes despite having lower fasting glucose.[31] In our cohort study, most patients with FGCV >100% had experience of glycemic emergency such as hyperglycemic hyperosmolar state or diabetic ketoacidosis or hypoglycemia episodes. We also noticed that the FGCV was higher in our analytic cohort compared with other Asian populations.[39,40] On the other hand, this observed phenomenon also highlighted the importance of higher GV in the lower fasting glucose group augmenting the risk for future PAD, and provided the possible target therapeutics.

High GV contributes to the development of chronic diabetes complications, especially MALEs and MACEs; therefore, good control of blood glucose levels and the maintenance of stable GV may reduce PAD and improve clinical outcomes for patients with T2D.

Limitations

This study has several limitations. First, diseases in the National Taiwan University Hospital-Integrated Medical Database were identified using *International Classification of Diseases*, *Ninth Revision and Tenth Revision*, *Clinical Modification* (*ICD-9-CM* and *ICD-10-CM*) codes and thus relied on the accuracy of the database. In addition, hemodynamics data and imaging studies were available in the database and provided support for the diagnostic results. The quality of integrated big data based on the electronic health records were assured.[41] Second, patients with asymptomatic or mild PAD symptoms may not have been diagnosed, leading to the underestimation of PAD incidence. Third, this study was a retrospective, observational, database study, and numerous confounding factors may have influenced our results. Although we attempted to adjust for confounders using the multivariate Cox models, additional unexplored confounding factors likely exist. Fourth, we only considered those prescriptions being used at the time of the initial exam rather than applying a time-varying design in which prescriptions were reevaluated at each follow-up. Fifth, impossibility to measure glucose variability was a frequent cause of exclusion from this study. Some patients might not have attended regular follow-ups at our clinics or may have been referred to other medical facilities, which

may have introduced some selection bias, missed outcomes, and other difficult to assess variability. Last, this was a retrospective cohort study.

CONCLUSIONS

In patients with T2D, higher GV led to significantly increased risks of MALEs compared with lower GV, driven largely by the increased development of PAD and CLI. Patients with increased GV were also associated with increased risks of MACE development, nonfatal stroke, nonfatal myocardial infarction, and death from any cause. The benefits of maintaining stable glycemic levels for improving clinical outcomes appear to be prominent. However, because this was an observational retrospective study, future larger, prospective, and multicenter prospective registries with longer follow-up are needed to validate these results.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S6

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SUPPLEMENTAL MATERIAL

Table S1. Baseline patients' characteristics with FGCV

	FGCV			
	Q1 (0%-9.00%)	Q2 (9.01%-14.60%)	Q3 (14.61%-23.69%)	Q4 (23.70%-189.27%)
N	10,872 (25.16)	10,970 (25.39)	10,711 (24.79)	10,653 (24.66)
Age (yr)	67.46 (9.67)	67.01 (9.67)	67.05 (9.77)	67.30 (10.17)
Male	5,352 (49.23)	5,818 (53.04)	5,678 (53.01)	5,758 (54.05)
Baseline BMI (kg/m2)	67.46 (9.67)	67.01 (9.67)	67.05 (9.77)	67.30 (10.17)
Hypertension	2,620 (24.10)	2,168 (19.76)	1,647 (15.38)	1,358 (12.75)
CAD	1,156 (10.63)	945 (8.61)	787 (7.35)	644 (6.05)
Baseline FPG (mg/dL)	117.14 (24.36)	127.99 (27.99)	140.0 (41.45)	160.60 (75.65)
Baseline HbA1c (%)	6.47 (0.89)	6.86 (1.00)	7.36 (1.33)	8.04 (1.82)
Baseline eGFR (mL/min/1.73 m2)	71.49 (26.59)	72.10 (27.68)	69.89 (29.72)	62.54 (32.83)
Medication				
Antiplatelet	3,725 (34.26)	4,261 (38.84)	4,537 (42.36)	4,621 (43.38)
Anticoagulant	677 (6.23)	686 (6.25)	695 (6.49)	774 (7.27)
CCB	5,116 (47.06)	5,709 (52.04)	5,983 (55.86)	6,259 (58.75)
Beta-blocker	3,752 (34.51)	4,152 (37.85)	4,164 (38.88)	4,471 (41.97)
ACEI/ARB	5,299 (48.74)	6,267 (57.13)	6,577 (61.40)	6,441 (60.46)
Diuretics	2,388 (21.96)	2,843 (25.92)	3,437 (32.09)	4,613 (43.30)
Statin	4,985 (45.85)	5,856 (53.38)	5,916 (55.23)	5,475 (51.39)
Insulin	1,096 (10.08)	1,613 (14.70)	3,151 (29.42)	6,146 (57.69)
Metformin	5,437 (50.01)	8,197 (74.72)	8,415 (78.56)	7,483 (70.24)

SGLT-2 inhibitor	543 (4.99)	1,342 (12.23)	1,937 (18.08)	1,609 (15.10)
DPP4 inhibitor	2,316 (21.30)	4,717 (43.00)	6,421 (59.95)	6,879 (64.57)
Sulphonylurea	1,651 (15.19)	4,405 (40.15)	6,698 (62.53)	6,810 (63.93)
TZD	413 (3.80)	1,159 (10.57)	2,050 (19.14)	2,303 (21.62)
GLP-1 agonist	23 (0.21)	88 (0.80)	271 (2.53)	402 (3.77)

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; BMI: body mass index; CAD, coronary artery disease; FPG, fasting glucose; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SGLT-2 inhibitor, sodium-glucose co-transporter-2 inhibitor; DPP4 inhibitor, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinediones; GLP-1 agonist, glucagon like peptide-1 agonist.

Table S2. Baseline characteristics of patients with and without missing values

	Missing HbA1c and/or fasting glucose (N=25883)		**Enrolled cohort (N=45436)**		**P value**
Age, mean (SD)	68.59	(10.12)	67.33	(9.87)	<.0001
Male (%)	13190	(50.96)	23797	(52.37)	0.0364
Baseline BMI	25.31	(4.36)	25.52	(4.35)	<.0001
Hypertension (%)	1,443	(5.58)	8,020	(17.65)	<.0001
CAD (%)	720	(2.78)	3,594	(7.91)	<.0001
Baseline FG, mean (SD)	138.40	(58.13)	136.40	(49.74)	0.011
Baseline HbA1C, mean (SD)	7.31	(1.60)	7.18	(1.44)	<.0001
Baseline eGFR, mean (SD)	64.96	(32.20)	68.62	(29.79)	<.0001
Medication					
Antiplatelet (%)	3,834	(14.81)	17,897	(39.39)	<.0001
Anticoagulant (%)	485	(1.87)	2,988	(6.58)	<.0001
CCB (%)	5,776	(22.32)	24,179	(53.22)	<.0001
Beta-blocker (%)	3,418	(13.21)	17,240	(37.94)	<.0001
ACEI/ARB (%)	4,506	(17.41)	25,517	(56.16)	<.0001
Diuretics (%)	3,310	(12.79)	14,066	(30.96)	<.0001
Statin (%)	2,642	(10.21)	22,861	(50.31)	<.0001
Insulin (%)	5,421	(20.94)	12,965	(28.53)	<.0001
Metformin (%)	4,777	(18.46)	30,528	(67.19)	<.0001
SGLT-2 inhibitor (%)	236	(0.91)	5,511	(12.13)	<.0001

DDP4 inhibitor (%)	3,180	(12.29)	21,028	(46.28)	<.0001
Sulphonylurea (%)	3,216	(12.43)	20,314	(44.71)	<.0001
TZD (%)	488	(1.89)	6,083	(13.39)	<.0001
GLP-1 agonist (%)	22	(0.08)	796	(1.75)	<.0001

BMI: body mass index; CAD, coronary artery disease; FPG, fasting glucose; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SGLT-2 inhibitor, sodium-glucose co-transporter-2 inhibitor; DPP4 inhibitor, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinediones; GLP-1 agonist, glucagon like peptide-1 agonist.

Table S3. Number of visits for the glycemic variability parameters

	Min	Average	Max
HVS			
Number of visits	2	13.38	75
FGCV			
Number of visits	2	14.27	107

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score

Table S4. Adjusted hazard ratios for MACE and MALE across quartiles of glycemic variability by FGCV

				Model 1		Model 2		Model 3	
Outcome	Group	No.	Event (%)	HR (95% C.I.)	p	HR (95% C.I.)	p	HR (95% C.I.)	p
Total mortality	FGCV_Q1	10,872	1,009 (9.28)	ref.		ref.		ref.	
	FGCV_Q2	10,970	1,039 (9.47)	0.90 (0.82 - 0.98)	0.016	0.92 (0.83 - 1.01)	0.094	1.03 (0.94 - 1.14)	0.509
	FGCV_Q3	10,711	1,433 (13.38)	1.24 (1.15- 1.35)	<0.001	1.28 (1.17 - 1.41)	<0.001	1.51 (1.37 - 1.66)	<0.001
	FGCV_Q4	10,653	2,667 (25.04)	2.58 (2.40 - 2.78)	<0.001	2.39 (2.18 - 2.61)	<0.001	2.69 (2.45 - 2.95)	<0.001
MACE	FGCV_Q1	10,872	657 (6.04)	ref.		ref.		ref.	
	FGCV_Q2	10,970	799 (7.28)	1.13 (1.01 - 1.25)	0.026	1.05 (0.94 - 1.18)	0.352	0.97 (0.87 - 1.09)	0.649
	FGCV_Q3	10,711	993 (9.27)	1.42 (1.29 - 1.57)	<0.001	1.25 (1.13 - 1.40)	<0.001	1.10 (0.99 - 1.23)	0.092
	FGCV_Q4	10,653	1,365 (12.81)	2.12 (1.93 - 2.33)	<0.001	1.60 (1.44 - 1.79)	<0.001	1.40 (1.25 - 1.56)	<0.001
Cardiac mortality	FGCV_Q1	10,872	175 (1.61)	ref.		ref.		ref.	
	FGCV_Q2	10,970	186 (1.70)	0.92 (0.74 - 1.13)	0.399	0.89 (0.70 - 1.12)	0.315	0.96 (0.76 - 1.22)	0.751
	FGCV_Q3	10,711	236 (2.20)	1.16 (0.95 - 1.41)	0.140	1.04 (0.83 - 1.30)	0.726	1.16 (0.92 - 1.46)	0.218
	FGCV_Q4	10,653	404 (3.79)	2.25 (1.88 - 2.68)	<0.001	1.56 (1.25 - 1.94)	<0.001	1.65 (1.32 - 2.07)	<0.001
AMI	FGCV_Q1	10,872	207 (1.90)	ref.		ref.		ref.	
	FGCV_Q2	10,970	253 (2.31)	1.12 (0.93 - 1.35)	0.217	1.01 (0.84 - 1.23)	0.893	0.84 (0.69 - 1.02)	0.076
	FGCV_Q3	10,711	338 (3.16)	1.52 (1.28 - 1.81)	<0.001	1.26 (1.05 - 1.51)	0.015	0.93 (0.77 - 1.13)	0.461
	FGCV_Q4	10,653	472 (4.43)	2.30 (1.95 - 2.70)	<0.001	1.57 (1.30 - 1.89)	<0.001	1.20 (0.99 - 1.45)	0.070
Ischemic stroke	FGCV_Q1	10,872	337 (3.10)	ref.		ref.		ref.	
	FGCV_Q2	10,970	398 (3.63)	1.12 (0.97 - 1.30)	0.123	1.05 (0.90 - 1.23)	0.515	0.95 (0.82 - 1.12)	0.557
	FGCV_Q3	10,711	470 (4.39)	1.35 (1.17 - 1.55)	<0.001	1.21 (1.04 - 1.41)	0.015	1.05 (0.90 - 1.23)	0.532
	FGCV_Q4	10,653	618 (5.80)	1.86 (1.63 - 2.13)	<0.001	1.52 (1.30 - 1.77)	<0.001	1.31 (1.12 - 1.54)	<0.001

MALE	FGCV_Q1	10,872	584 (5.37)	ref.		ref.		ref.	
	FGCV_Q2	10,970	691 (6.30)	1.10 (0.98 - 1.22)	0.106	1.01 (0.90 - 1.14)	0.844	0.99 (0.88 - 1.11)	0.861
	FGCV_Q3	10,711	935 (8.73)	1.52 (1.37 - 1.68)	<0.001	1.32 (1.18 - 1.48)	<0.001	1.24 (1.10 - 1.39)	<0.001
	FGCV_Q4	10,653	1,314 (12.33)	2.32 (2.10 - 2.56)	<0.001	1.72 (1.54 - 1.92)	<0.001	1.57 (1.40 - 1.76)	<0.001
PAD	FGCV_Q1	10,872	583 (5.36)	ref.		ref.		ref.	
	FGCV_Q2	10,970	691 (6.30)	1.10 (0.98 - 1.23)	0.1000	1.01 (0.90 - 1.14)	0.818	0.99 (0.88 - 1.12)	0.889
	FGCV_Q3	10,711	935 (8.73)	1.52 (1.37 - 1.69)	<0.001	1.33 (1.19 - 1.48)	<0.001	1.24 (1.11 - 1.39)	<0.001
	FGCV_Q4	10,653	1,312 (12.32)	2.32 (2.10 - 2.56)	<0.001	1.72 (1.54 - 1.92)	<0.001	1.57 (1.40 - 1.76)	<0.001
CLI	FGCV_Q1	10,872	43 (0.40)	ref.		ref.		ref.	
	FGCV_Q2	10,970	49 (0.45)	1.01 (0.67 - 1.52)	0.974	0.87 (0.57 - 1.32)	0.510	0.83 (0.54 - 1.28)	0.407
	FGCV_Q3	10,711	104 (0.97)	2.15 (1.51 - 3.07)	<0.001	1.47 (1.01 - 2.14)	0.042	1.34 (0.91 - 1.96)	0.142
	FGCV_Q4	10,653	250 (2.35)	5.74 (4.16 - 7.94)	<0.001	2.53 (1.76 - 3.62)	<0.001	2.19 (1.51 - 3.17)	<0.001

Model 1: no adjust;

Model 2: adjusted for age, sex, baseline BMI, hypertension, CAD, average FG, average HbA1c, baseline eGFR;

Model 3: adjusted for model 2 plus medications (metformin, SGLT2 inhibitor, DDP4 inhibitor, GLP-1 agonist)

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; BMI: body mass index; CAD, coronary artery disease; FPG, fasting glucose; eGFR, estimated glomerular filtration rate; CCB, calcium channel blocker; ACEI/ARB, angiotensin converting enzyme inhibitor/angiotensin receptor blocker; SGLT-2 inhibitor, sodium-glucose co-transporter-2 inhibitor; DPP4 inhibitor, dipeptidyl peptidase 4 inhibitor; TZD, thiazolidinediones; GLP-1 agonist, glucagon like peptide-1 agonist.

Table S5. The results of HbA1c variability with SD for outcomes

Outcome	Group	Patient No.	event	(%)	HR	95% C.I.	p value
Total mortality	HbA1c-SD_Q1	10,537	1,120	(10.63)	ref.		
	HbA1c-SD_Q2	10,495	1,178	(11.22)	0.89	(0.81- 0.97)	0.0105
	HbA1c-SD_Q3	10,492	1,489	(14.19)	0.93	(0.85- 1.03)	0.1488
	HbA1c-SD_Q4	10,487	2,059	(19.63)	1.17	(1.06- 1.29)	0.0021
Cardiac mortality	HbA1c-SD_Q1	10,537	215	(2.04)	ref.		
	HbA1c-SD_Q2	10,495	222	(2.12)	0.78	(0.63- 0.96)	0.0203
	HbA1c-SD_Q3	10,492	235	(2.24)	0.60	(0.48- 0.75)	<.0001
	HbA1c-SD_Q4	10,487	309	(2.95)	0.69	(0.55 - 0.88)	0.0027
Non-cardiac mortality	HbA1c-SD_Q1	10,537	905	(8.59)	ref.		
	HbA1c-SD_Q2	10,495	956	(9.11)	0.91	(0.82- 1.01)	0.0653
	HbA1c-SD_Q3	10,492	1,254	(11.95)	1.02	(0.92- 1.13)	0.7381
	HbA1c-SD_Q4	10,487	1,750	(16.69)	1.29	(1.16- 1.45)	<.0001
MACE	HbA1c-SD_Q1	10,537	668	(6.34)	ref.		
	HbA1c-SD_Q2	10,495	861	(8.20)	1.01	(0.91- 1.13)	0.8133
	HbA1c-SD_Q3	10,492	1,036	(9.87)	0.98	(0.87- 1.10)	0.6949
	HbA1c-SD_Q4	10,487	1,310	(12.49)	1.14	(1.01- 1.28)	0.0399
AMI	HbA1c-SD_Q1	10,537	195	(1.85)	ref.		
	HbA1c-SD_Q2	10,495	278	(2.65)	1.00	(0.82- 1.22)	0.9980
	HbA1c-SD_Q3	10,492	358	(3.41)	0.93	(0.76- 1.14)	0.4999
	HbA1c-SD_Q4	10,487	489	(4.66)	1.11	(0.89- 1.37)	0.3524
Ischemic stroke	HbA1c-SD_Q1	10,537	315	(2.99)	ref.		

	HbA1c-SD_Q2	10,495	424	(4.04)	1.10	(0.94- 1.29)	0.2309
	HbA1c-SD_Q3	10,492	516	(4.92)	1.17	(0.99- 1.37)	0.0620
	HbA1c-SD_Q4	10,487	613	(5.85)	1.30	(1.09- 1.55)	0.0031
MALE	HbA1c-SD_Q1	10,537	605	(5.74)	ref.		
	HbA1c-SD_Q2	10,495	747	(7.12)	1.01	(0.90- 1.13)	0.8932
	HbA1c-SD_Q3	10,492	1,021	(9.73)	1.14	(1.02- 1.28)	0.0262
	HbA1c-SD_Q4	10,487	1,132	(10.79)	1.19	(1.05- 1.35)	0.0077
PAD	HbA1c-SD_Q1	10,537	605	(5.74)	ref.		
	HbA1c-SD_Q2	10,495	746	(7.11)	1.01	(0.90- 1.13)	0.9135
	HbA1c-SD_Q3	10,492	1,020	(9.72)	1.14	(1.01- 1.28)	0.0279
	HbA1c-SD_Q4	10,487	1,131	(10.78)	1.19	(1.05- 1.35)	0.0083
CLI	HbA1c-SD_Q1	10,537	52	(0.49)	ref.		
	HbA1c-SD_Q2	10,495	69	(0.66)	0.82	(0.56- 1.20)	0.2975
	HbA1c-SD_Q3	10,492	118	(1.12)	0.82	(0.57- 1.18)	0.2825
	HbA1c-SD_Q4	10,487	217	(2.07)	1.09	(0.75- 1.58)	0.6580

Model3 : model2+ medication (insulin, metformin, SGLT2inhibitor, DDP4 inhibitor, GLP-1 agonist

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; MALE, major adverse limb events (MALEs); MACEs, major adverse cardiovascular events; AMI, acute myocardial infarction; PAD, peripheral arterial disease; CLI, critical limb ischemia

Table S6. The results of HbA1c variability with CV for outcomes

Outcome	Group	Patient No.	event	(%)	HR	95% C.I.	p value
Total mortality	HbA1c-CV_Q1	10,543	1,121	(10.63)	ref.		
	HbA1c-CV_Q2	10,489	1,107	(10.55)	0.83	(0.75- 0.91)	<.0001
	HbA1c-CV_Q3	10,490	1,510	(14.39)	0.93	(0.84- 1.02)	0.1001
	HbA1c-CV_Q4	10,489	2,108	(20.10)	1.17	(1.06- 1.29)	0.0017
Cardiac mortality	HbA1c-CV_Q1	10,543	212	(2.01)	ref.		
	HbA1c-CV_Q2	10,489	209	(1.99)	0.74	(0.60- 0.91)	0.0050
	HbA1c-CV_Q3	10,490	247	(2.35)	0.63	(0.50- 0.78)	<.0001
	HbA1c-CV_Q4	10,489	313	(2.98)	0.69	(0.55- 0.87)	0.0014
Non-cardiac mortality	HbA1c-CV_Q1	10,543	909	(8.62)	ref.		
	HbA1c-CV_Q2	10,489	898	(8.56)	0.85	(0.76- 0.94)	0.0022
	HbA1c-CV_Q3	10,490	1,263	(12.04)	1.00	(0.90- 1.11)	0.9659
	HbA1c-CV_Q4	10,489	1,795	(17.11)	1.29	(1.16- 1.44)	<.0001
MACE	HbA1c-CV_Q1	10,543	661	(6.27)	ref.		
	HbA1c-CV_Q2	10,489	826	(7.87)	0.97	(0.87- 1.09)	0.6177
	HbA1c-CV_Q3	10,490	1,060	(10.10)	1.00	(0.90- 1.12)	0.9489
	HbA1c-CV_Q4	10,489	1,328	(12.66)	1.17	(1.04- 1.31)	0.0105
AMI	HbA1c-CV_Q1	10,543	195	(1.85)	ref.		
	HbA1c-CV_Q2	10,489	274	(2.61)	1.01	(0.83- 1.23)	0.9447
	HbA1c-CV_Q3	10,490	359	(3.42)	0.94	(0.77- 1.15)	0.5424
	HbA1c-CV_Q4	10,489	492	(4.69)	1.15	(0.94- 1.41)	0.1796
Ischemic stroke	HbA1c-CV_Q1	10,543	309	(2.93)	ref.		

	HbA1c-CV_Q2	10,489	400	(3.81)	1.06	(0.90- 1.24)	0.5176
	HbA1c-CV_Q3	10,490	533	(5.08)	1.22	(1.04- 1.43)	0.0149
	HbA1c-CV_Q4	10,489	626	(5.97)	1.36	(1.15- 1.61)	0.0004
MALE	HbA1c-CV_Q1	10,543	596	(5.65)	ref.		
	HbA1c-CV_Q2	10,489	756	(7.21)	1.03	(0.92- 1.16)	0.6236
	HbA1c-CV_Q3	10,490	1,018	(9.70)	1.12	(1.00- 1.26)	0.0508
	HbA1c-CV_Q4	10,489	1,135	(10.82)	1.17	(1.03- 1.32)	0.0127
PAD	HbA1c-CV_Q1	10,543	596	(5.65)	ref.		
	HbA1c-CV_Q2	10,489	755	(7.20)	1.03	(0.92- 1.15)	0.6419
	HbA1c-CV_Q3	10,490	1,017	(9.69)	1.12	(1.00- 1.26)	0.0537
	HbA1c-CV_Q4	10,489	1,134	(10.81)	1.17	(1.03- 1.32)	0.0135
CLI	HbA1c-CV_Q1	10,543	55	(0.52)	ref.		
	HbA1c-CV_Q2	10,489	66	(0.63)	0.77	(0.52- 1.12)	0.1663
	HbA1c-CV_Q3	10,490	122	(1.16)	0.77	(0.54- 1.10)	0.1530
	HbA1c-CV_Q4	10,489	213	(2.03)	1.01	(0.71- 1.45)	0.9499

Model 3: adjusted for age, sex, baseline BMI, hypertension, CAD, average FG, average HbA1c, baseline eGFR plus medications (metformin, SGLT2 inhibitor, DDP4 inhibitor, GLP-1 agonist)

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; MALE, major adverse limb events (MALEs); MACEs, major adverse cardiovascular events; AMI, acute myocardial infarction; PAD, peripheral arterial disease; CLI, critical limb ischemia

Table S7. Pairwise comparison for log-rank test of FGCV

	MACE	MALE
FGCV_Q1 v.s. FGCV_Q2	0.0177	0.1053
FGCV_Q1 v.s. FGCV_Q3	<.0001	<.0001
FGCV_Q1 v.s. FGCV_Q4	<.0001	<.0001
FGCV_Q2 v.s. FGCV_Q3	<.0001	<.0001
FGCV_Q2 v.s. FGCV_Q4	<.0001	<.0001
FGCV_Q3 v.s. FGCV_Q4	<.0001	<.0001

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; MALE, major adverse limb events (MALEs); MACEs, major adverse cardiovascular events

Table S8. Pairwise comparison for log-rank test of HVS

	MACE	MALE
HVS_Q1 v.s. HVS_Q2	0.0090	0.1264
HVS_Q1 v.s. HVS_Q3	<.0001	<.0001
HVS_Q1 v.s. HVS_Q4	<.0001	<.0001
HVS_Q2 v.s. HVS_Q3	<.0001	<.0001
HVS_Q2 v.s. HVS_Q4	<.0001	<.0001
HVS_Q3 v.s. HVS_Q4	<.0001	<.0001

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; MALE, major adverse limb events (MALEs); MACEs, major adverse cardiovascular events

Figure S1. Scatter plot along with Pearson's correlation test.

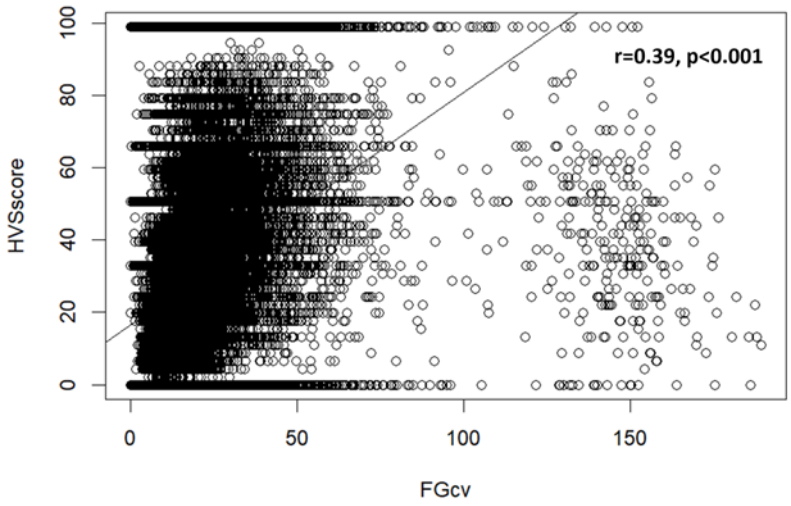
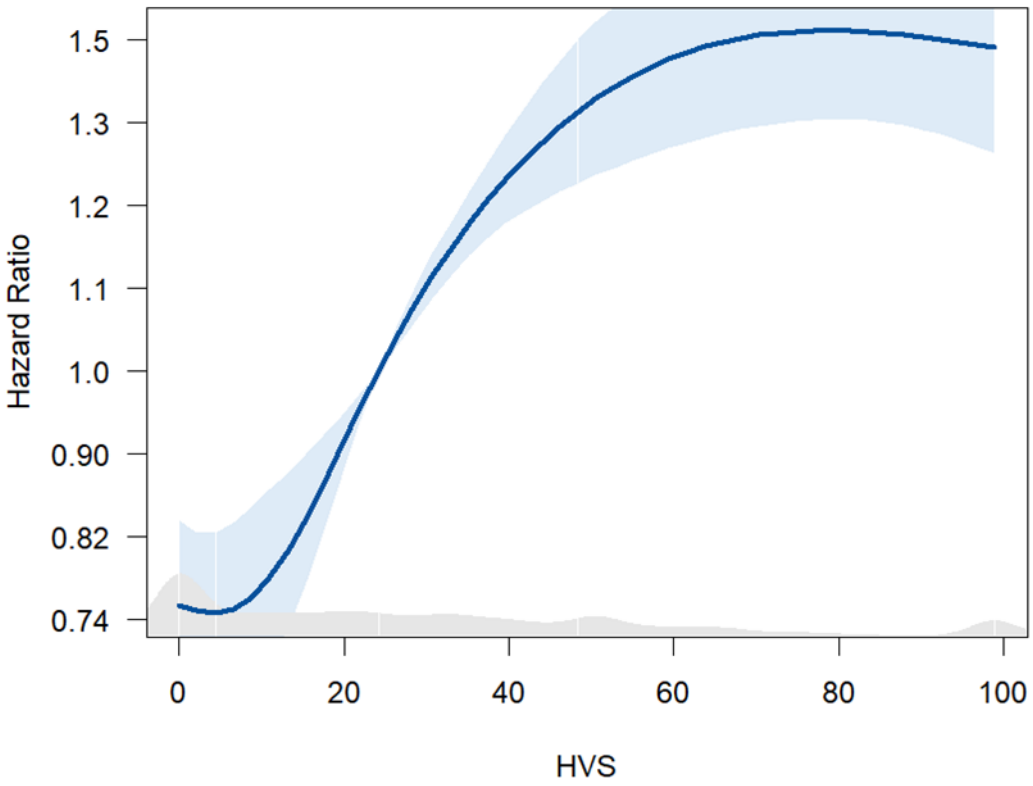


Figure S2. Restrictive cubic spline (RCS) for non-linear hazard ratio of MALE (A), MACE (B), CLI (C), and cardiac mortality (D) stratified by HVS.

(A)



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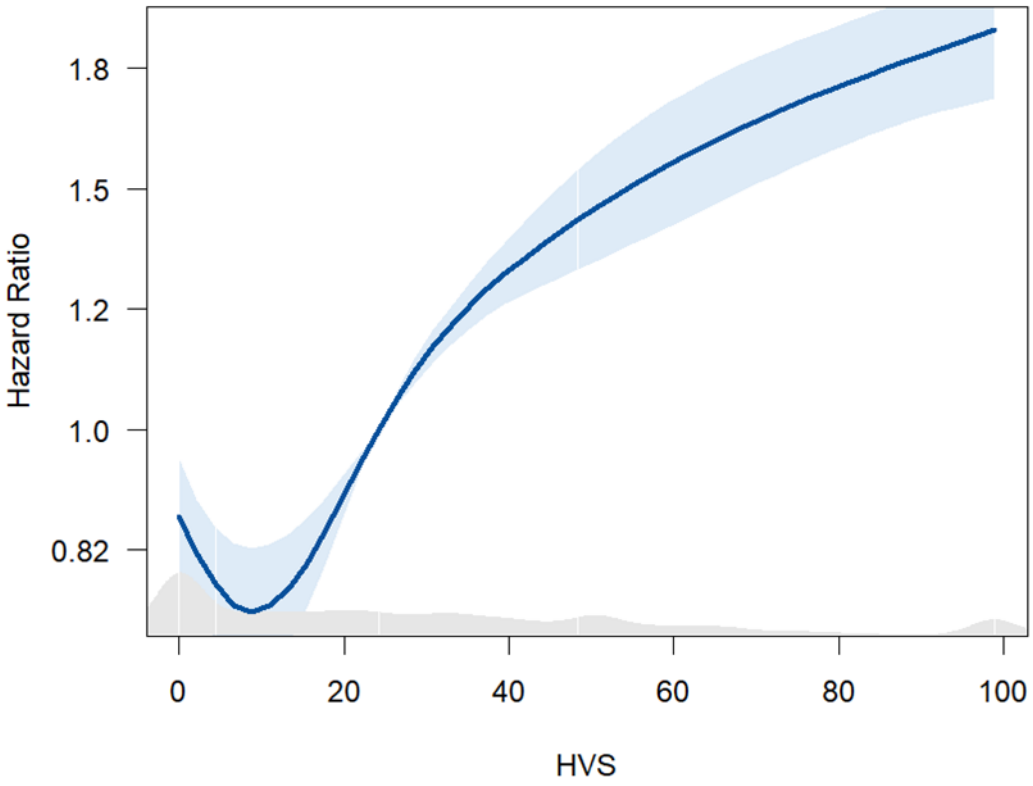
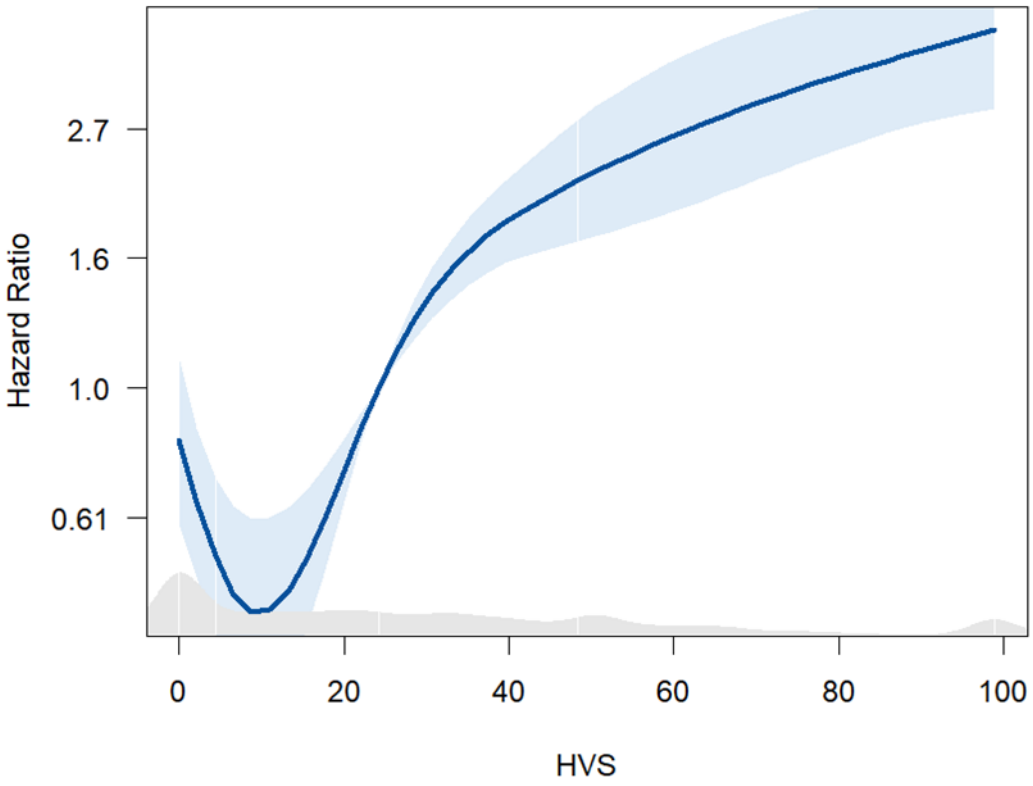
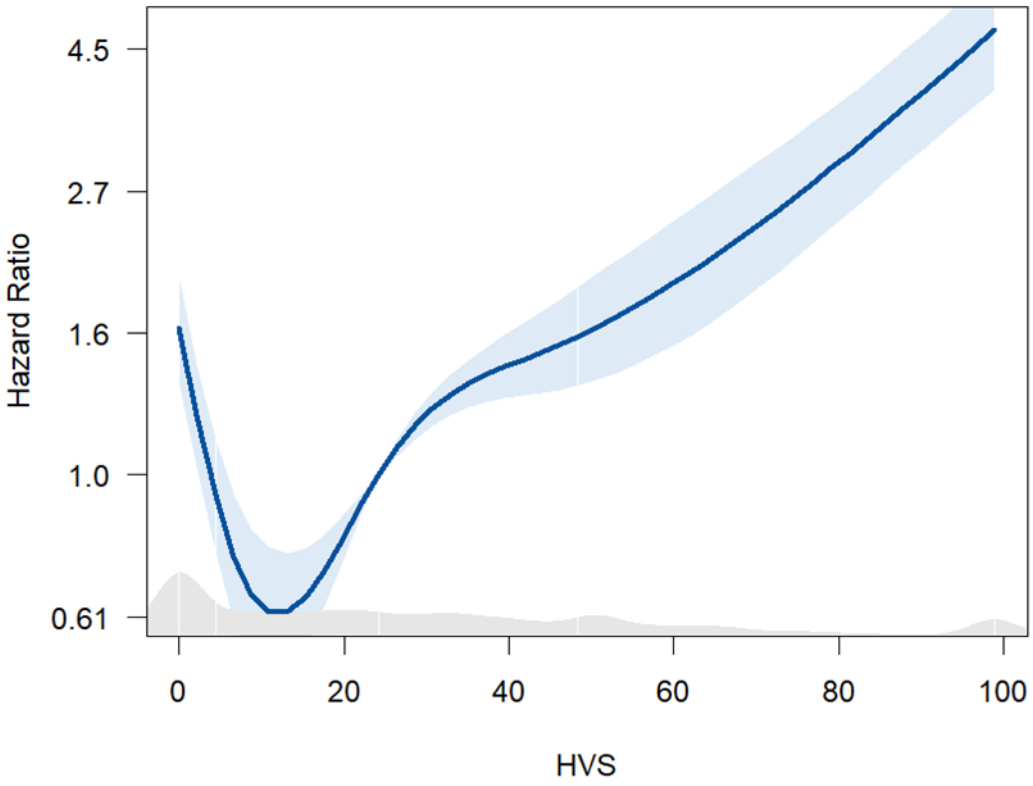


(C)



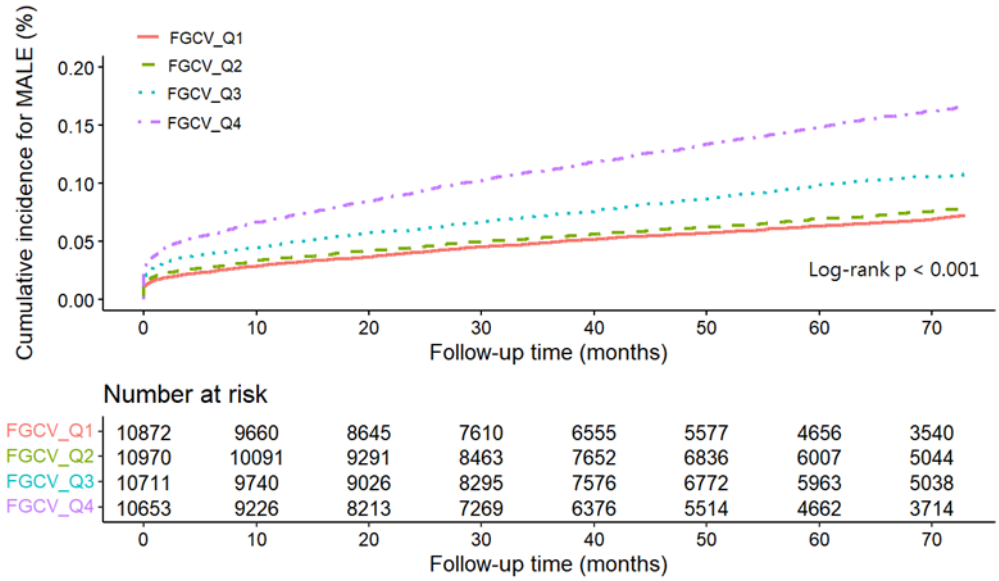
(D)



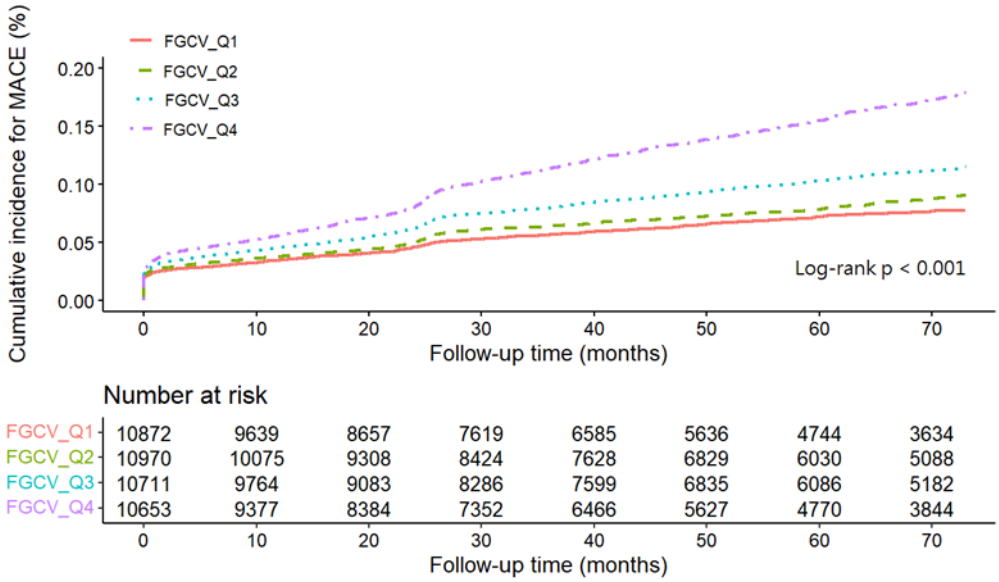
MALE, major adverse limb event; MACE, major adverse cardiovascular event; CLI, critical limb ischemia; HVS, HbA1c variability score.

Figure S3. Cumulative event incidence for MALEs (A) and MACEs (B) stratified by FGCV.

(A)

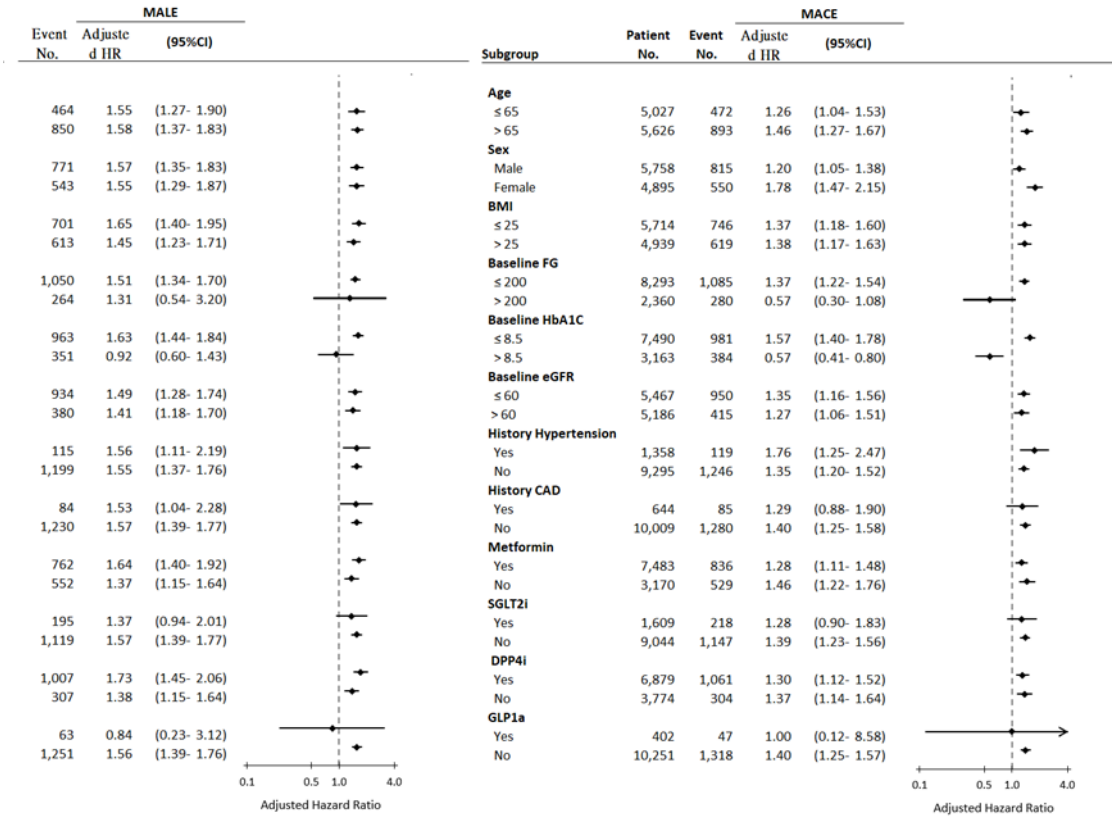


(B)



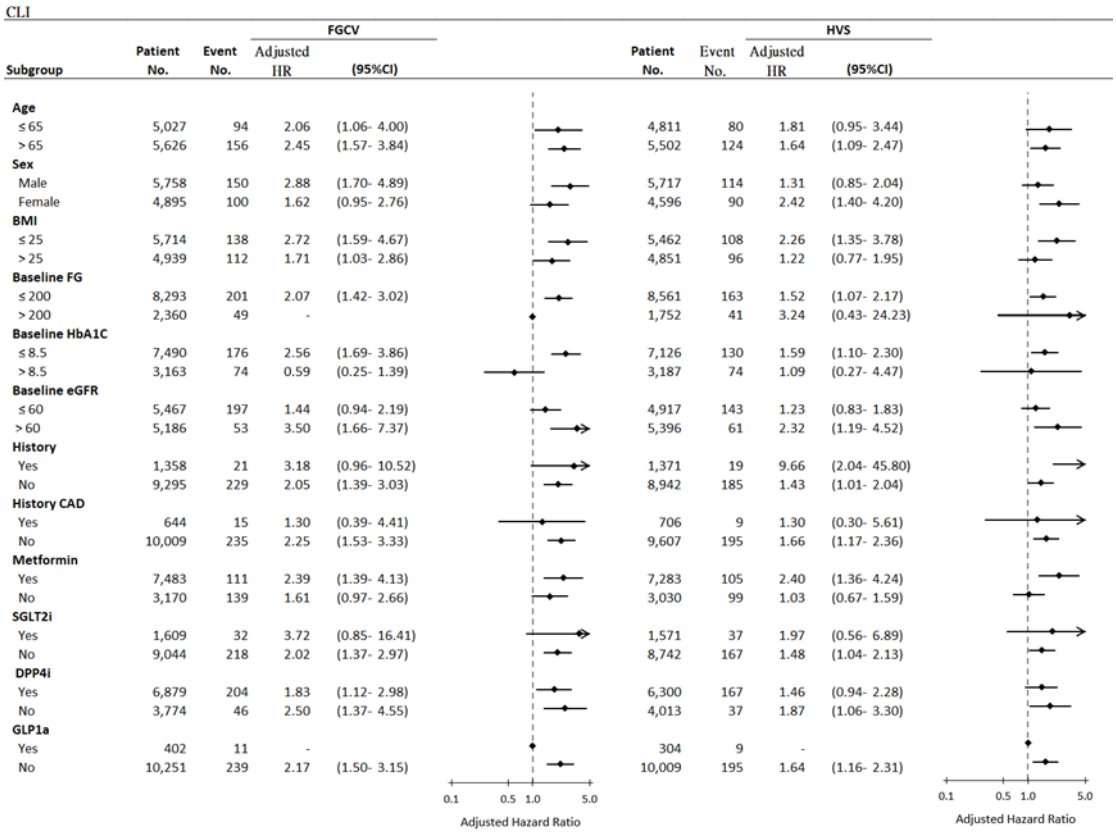
MALE, major adverse limb event; MACE, major adverse cardiovascular event; FGCV, fasting glucose coefficient of variability.

Figure S4. Subgroup analyses for MALEs (A) and MACEs (B) stratified by FGCV.



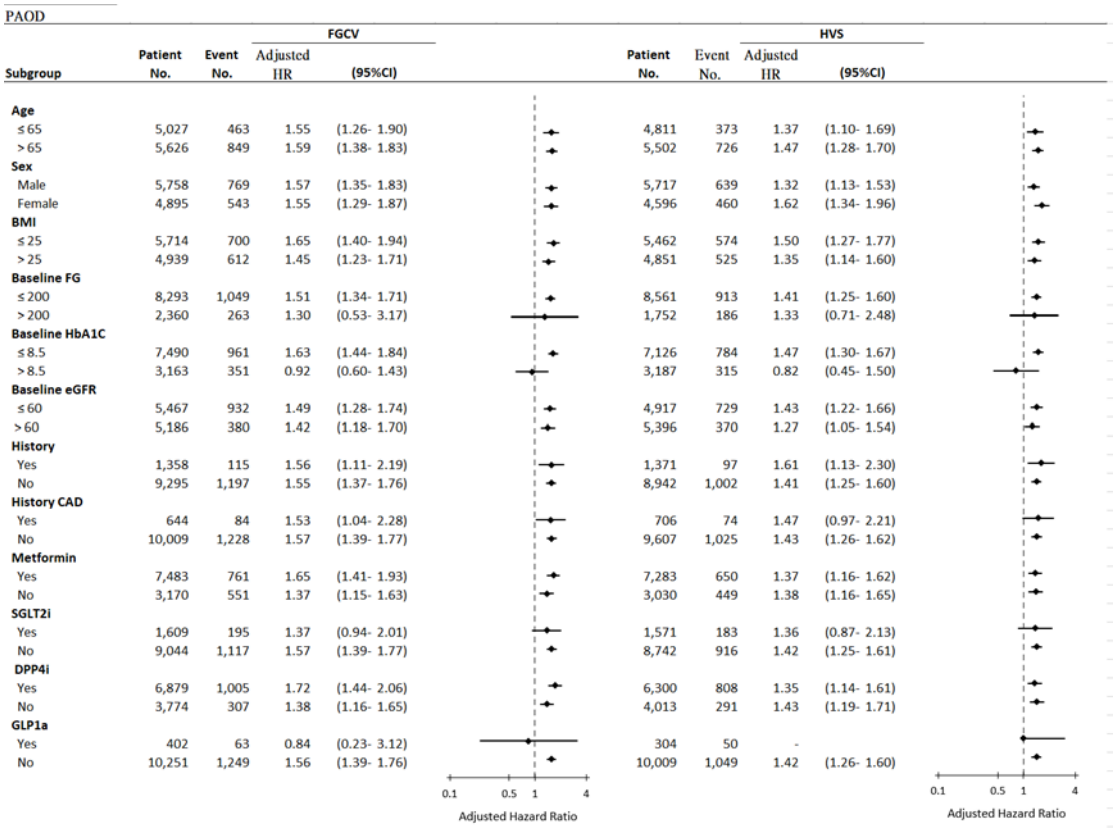
MACE, major adverse cardiac event; MALE, major adverse limb event; FGCV, fasting glucose coefficient of variability.

Figure S5. Subgroup analyses for CLI stratified by FGCV (A) and HVS (B).



CLI, critical limb ischemia; FGCV, fasting glucose coefficient of variability; HVS, HbA1c variability score.

Figure S6. Subgroup analyses for PAD stratified by FGCV (A) and HVS (B).



PAD, peripheral artery disease; FGCV, fasting glucose coefficient of variability; HVS, HbA1c variability score.