Higher Long-term Visit-to-Visit Glycemic Variability Predicts New-Onset Atrial Fibrillation in Patients with Diabetes Mellitus

Jung-Chi Hsu (✉ cactus146@gmail.com)

Saint Mary's Hospital Luodong

Yen-Yun Yang

National Taiwan University Hospital

Shu-Lin Chuang

National Taiwan University Hospital

Chih-Chieh Yu

National Taiwan University Hospital

Lian-Yu Lin

National Taiwan University Hospital

Research Article

Keywords: glycemic variability, atrial fibrillation, diabetes mellitus

Posted Date: June 9th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-588082/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Version of Record: A version of this preprint was published at Cardiovascular Diabetology on July 23rd, 2021. See the published version at <https://doi.org/10.1186/s12933-021-01341-3>.

Abstract

Background

Atrial fibrillation (AF) is prevalent in patients with type 2 diabetes mellitus (T2DM). Glycemic variability (GV) is associated with risk of micro- and macrovascular diseases. However, whether the GV can increase the risk of AF remains unknown.

Methods

The cohort study used a database from National Taiwan University Hospital, a tertiary medical center in Taiwan. Between 2014 and 2019, a total of 27246 adult patients with T2DM were enrolled for analysis. Each individual was assessed to determine the coefficients of variability of fasting glucose (FGCV) and HbA1c variability score (HVS). The GV parameters were categorized into quartiles. Multivariate Cox regression models were employed to estimate the relationship between the GV parameters and the risk of AF, transient ischemic accident (TIA)/ischemic stroke and mortality in patients with T2DM.

Results

The incidence rates of AF and TIA/ischemic stroke were 21.31 and 13.71 per 1000 person-year respectively. The medium follow-up period was 70.7 months. In Cox regression model with full adjustment, the highest quartiles of FGCV was not associated with increased risk of AF (Hazard ratio (HR): 1.11, 95% confidence interval (CI): 0.96-1.29, $p=0.165$) or TIA/ischemic stroke (HR: 1.03, 95% CI: 0.82-1.29, $p=0.821$), but was associated with increased risk of total mortality (HR: 1.34, 95% CI: 1.13-1.60, $p<0.001$) and non-cardiac mortality (HR: 1.42, 95% CI: 1.17-1.72, $p<0.001$). The highest HVS was significantly associated with increased risk of AF (HR: 1.29, 95% CI: 1.12-1.48, $p<0.001$), total mortality (HR: 2.44, 95% CI: 2.04-2.91, $p<0.001$), cardiac mortality (HR: 1.48, 95% CI: 1.04-2.10, $p=0.028$) and non-cardiac mortality (HR: 2.83, 95% CI: 2.31-3.14, $p<0.001$) but was not associated with TIA/ischemic stroke (HR: 1.00, 95% CI: 0.79-1.26, $p=0.989$). The Kaplan-Meier analysis showed significantly higher risk of AF, cardiac and non-cardiac mortality according to the magnitude of GV(log-rank <0.001).

Conclusions

Higher GV is independently associated with the development of new-onset AF in patients with T2DM. Reducing GV may be a potential new therapeutic target to prevent AF.

Introduction

Atrial fibrillation (AF) is prevalent in patients with aging, congestive heart failure (CHF), hypertension (HTN), and diabetes mellitus (DM). Patients with type 2 diabetes mellitus (T2DM) carry an overall 35% higher risk of AF compared to general population, and increased blood glucose has a dose-response relationship with the incidence of AF. [1, 2] In molecular perspective, hyperglycemia has been proved to increase interstitial fibrosis of atrial tissue and intracellular calcium dysregulation, both of which contribute to the impairment of atrial tissue relaxation, atrial electrical and structural remodeling and finally leads to atrial fibrillation. [3]

Apart from focusing primarily on measurement of fasting plasma glucose (FG), hemoglobin A1c (HbA1c), advanced glycation end products (AGEs), glucagon-like peptide 1 (GLP-1), short-term glycemic variability within-days or months or even years have been considered as important risk factors for cardiovascular disease. [4] Glycemic fluctuation has been shown to over-activate oxidative stress and inflammation system, aggravating greater vascular damage and cardiomyopathy than that in chronic stable hyperglycemia. [4, 5] Increased glycemic variation (GV) also has adverse effect on autonomic function and increases the thrombotic properties of the platelets, which may be associated with higher incidence of major adverse cardiovascular event (MACE). [6, 7]

Previous studies have shown that patients with higher acute GV have more vulnerable plaques and poorer prognosis of acute coronary syndrome. [8, 9, 10] Short-term GV is also associated with increased mortality after cardiac procedure such as transcatheter aortic valve implantation. [11] Long-term GV was found to be associated with greater progression of coronary artery calcification in young adults. [12] High GV also causes left ventricular diastolic dysfunction and increased the risk of heart failure. [13, 14] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) study, GV was independently associated with the risks of cardiovascular event and all-cause mortality. [15]

Nevertheless, the majority of the studies regarding the effect of GV have focused on diabetic macro- and micro-vascular complications. Whether GV is associated with the development of AF is not known. Investigating the contribution of GV on the development of AF may advance our understanding of how dysfunction in glucose homeostasis impacts atrial remodeling. In this cohort study, we plan to investigate the association of long-term GV with the incidence of AF and related cardiovascular outcomes in a group of patients with T2DM.

Methods

Study Population and Data Collection

The study was approved by the Institutional Review Board (IRB) of National Taiwan University Hospital. The study database was from National Taiwan University Hospital integrated Medical Database (NTUH-IMD) which was composed of detailed medical information from a tertiary medical center in Taiwan. Since AF is prevalent in patients with older age, we enrolled those with age above 50 years and diagnosed with T2DM at the National Taiwan University Hospital from January 1, 2014, to December 31, 2019. Patients with previous AF or lost to follow-up (defined as an absence of follow-up at the outpatient clinics between Oct. 1st to Dec. 31, 2019 since we followed patients at least every three months) were excluded. For simplicity, patients who had severe end organ damage including history of congestive heart failure (CHF) or above stage 3 chronic kidney disease (CKD) were also excluded. Baseline characteristics including body mass index (BMI), hypertension (HTN), hyperlipidemia, coronary artery disease (CAD), acute coronary syndrome (ACS), myocardial infarction (MI), chronic obstructive pulmonary disease (COPD), peripheral arterial occlusive disease (PAOD) were obtained from the electronic health records (EHRs). Estimated glomerular filtration rate (eGFR) was calculated by modification of diet in renal disease (MDRD) equation. Prescription information were categorized into antiarrhythmic agents, calcium channel blocker (CCB), beta-blocker, angiotensin converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), mineralocorticoid-receptor antagonist (MRA), anticoagulants including direct oral anticoagulant (DOAC) and warfarin, and anti-diabetic medications including insulin, metformin, sodium-glucose co-transporter-2 (SGLT2) inhibitor, dipeptidyl peptidase 4 (DPP4) inhibitor, sulphonylurea, repaglinide, acarbose, thiazolidinedione (TZD), glucagon like peptide-1 (GLP-1) agonist. The echocardiographic data including left atrium (LA) size, left ventricular ejection fraction (LVEF), left ventricular mass (LVM), and parameters of diastolic function were also assessed from the EHRs. The outcomes were AF, transient ischemic accident (TIA), ischemic stroke and mortality. Death events were also adjudicated by a central committee, and were separated to cardiac and noncardiac mortality. AF and its occurrence time were identified by the diagnosis code from either the EHRs or the standard 12-lead electrocardiogram. The index dates of outcomes were defined as the dates of diagnosis. All medical records were reviewed until their last clinical visit or death.

Glycemic Variability Measurement

We calculated two measures of GV for each individual: the coefficient variability of the mean FG (FGCV) and the HbA1c variability score (HVS). FG and HA1C were measured quarterly at visit-to-visit outpatient department. FG was measured in subjects who reported fasting more than 8 hours. The calculation of FG and HbA1c variability was from at least three successive measurements. Only patients having both FGCV and HVS were included for analysis. FGCV (%) was calculated as the standard deviation (SD) of FG divided by the mean FG, and then divided by the square root of the ratio of FG measurements n to $n-1$ ($\sqrt{n/(n-1)}$) to account for the influence of FG measurement number. [16, 17] HVS is the number of measures within an individual where the HbA1c has changed by $>0.5\%$ (5.5 mmol/mol) from the prior value, as a percentage of the total number of HbA1c measures between the diagnosis of diabetes and the outcome. In brief, HVS is a percentage of HbA1c fluctuation events ($\Delta > 0.5\%$). [18]

Statistical Analysis

Patients were categorized into four groups according to the quartiles of FGCV or HVS. Continuous variables were described as mean (SD) and categorical variables were reported as frequency (percentage). Differences among groups were tested by using chi square test for categorical variables and analysis of variance (ANOVA) test for continuous variables. Multivariate Cox proportional hazards models were constructed to assess the association of categorical and continuous measures. The relationship between GV and the development of diabetes complications was assessed by Cox regression from which hazard ratios (HRs) and 95% confidence intervals (CIs) were derived. The assumption of proportionality was validated by verifying the Schoenfeld residuals.

The semiparametric Cox regression models were sequentially adjusted for the following baseline covariates. The model 1 was crude model without any adjustment. The model 2 adjusted for age, gender (male as reference group), baseline BMI, history of HTN, COPD, CAD, PAOD and prior TIA/ischemic stroke, baseline FG, baseline HbA1c, and baseline estimated glomerular filtration rate (eGFR). The model 3 adjusted for model 2 plus three echocardiogram parameters including LA size, LVEF, LVM. Model 4 adjusted for model 3 plus the medications including antiplatelet, anticoagulant, CCB, betablocker, ACEI/ARB, diuretic, statin, insulin, metformin, SGLT2 inhibitor, DPP4 inhibitor, sulphonylurea, repaglinide, acarbose, TZD, GLP-1 agonist. Survival analyses were presented by using Kaplan-Meier curves and the significance of difference between curves were examined by log-rank test. All statistical analyses were performed using SAS statistical software package (version 9.4. SAS Institute Inc., Cary, NC, USA). A two-tailed p -value of less than 0.05 was considered statistically significant.

Results

Baseline Characteristics

The flowchart of patient selection was demonstrated in Fig. 1. A total of 74835 with T2DM diagnosis code between 2014 and 2019 were enrolled. Among them, 121 patients without firm evidence of T2DM (blood test, DM medications) and 1607 patients aged below 50 years were excluded. We excluded 1755 patients with pre-existing AF, 125 patients with severe CHF (ever hospitalization caused by acute decompensated heart failure), and 6054 patients with moderate or severe CKD ($\geq$ stage 3 CKD). We only included patients with both FGCV and HVS data, so 38628 patients who only had either FGCV or HVS data were excluded. We also excluded the patients with nonmeaningful variance FGCV = 0 or HVS = 0. Finally, a total of 27246 subjects were enrolled for further analysis. The patients were grouped according to the quartiles of either FGCV or HVS. The clinical,

biochemical and anthropometric characteristics were presented in Table 1. The subjects in the highest quartile of FGCV were older, had higher baseline FG and HbA1c, had worse baseline eGFR, were more likely to have PAOD and less likely to have HTN or CAD. The subjects in the highest quartile of HVS were more male gender, had less HTN, had higher baseline FG and HbA1c levels and lower baseline eGFR.

Over a median follow-up of 70.7 months, there were 2762 AF events (overall incidence rate 21.31 per 1000 person-year) and 1803 TIA/ischemic stroke events (overall incidence rate 13.71 per 1000 person-year). The incidence rates of AF for FGCV quartiles were 16.47, 17.66, 19.86, and 31.76 per 1000 person-year. The incidence rates of AF for HVS quartiles were 14.19, 19.30, 24.37, and 29.27 per 1000 person-year. The incidence rates of TIA/ischemic stroke for FGCV quartiles were 11.98, 11.52, 13.88, 17.66 per 1000 person-year. The incidence rates of TIA/ischemic stroke for HVS quartiles were 10.32, 15.83, 16.52, 15.63 per 1000 person-year. There were 3545 deaths in which 615 (17.35%) were cardiac causes.

Measures of Glycemic Variability and Outcomes

As shown in Table 2, in comparison with the first quartile of FGCV, the hazard ratios (HRs) across quartiles (second to fourth quartiles) for AF were 1.30 (95% CI: 1.16–1.45, $p < 0.001$), 1.64 (95% CI: 1.47–1.84, $p < 0.001$), and 1.97 (95% CI: 1.76–2.20, $p < 0.001$) in model 1 without adjustment. After model 2 and 3 adjustment, the fourth quartile remained significantly associated with the development of AF and the HRs were 1.74 (95% CI: 1.55–1.96, $p < 0.001$) and 1.47 (95% CI: 1.29–1.69, $p < 0.001$) for model 2 and 3 respectively. In fully adjusted model 4, the HRs for AF became insignificant (1.11, 95% CI: 0.96–1.29, $p = 0.165$). As for other outcomes, in fully adjusted model, the fourth quartile remained significant for total mortality (1.34, 95% CI: 1.13–1.60, $p < 0.001$) and non-cardiac mortality (1.42, 95% CI: 1.17–1.72, $p < 0.001$) but became insignificant for TIA/ischemic stroke (1.03, 95% CI: 0.82–1.29, $p = 0.821$) and cardiac mortality (1.08, 95% CI: 0.75–1.55, $p = 0.687$).

Also shown in Table 2, by using the first quartile of HVS as reference, the HRs for AF remained significant in the third (1.15, 95% CI: 1.00–1.32, $p = 0.044$) and fourth quartile (1.29, 95% CI: 1.12–1.48, $p < 0.001$) in fully adjusted model. As for other outcomes, in fully adjusted model, in comparison with the first quartile, all three quartiles were significantly associated with total mortality and non-cardiac mortality but only the fourth quartile remained significant for cardiac mortality (1.48, 95% CI: 1.04–2.10, $p = 0.0282$). For TIA/ischemic stroke, all quartiles were nonsignificant in fully adjusted model. Forest plot of HRs in fully adjusted models were demonstrated in Fig. 2A (FGCV) and 2B (HVS).

The results of Kaplan-Meier analysis were demonstrated in Fig. 3. As shown in Fig. 3, the probability of AF (3A), mortality (3B), non-cardiac mortality (3C) and cardiac mortality (3D) were significantly different across quartiles of HVS (All log-rank $p < 0.001$).

Discussion

Our study showed that a greater GV is associated with a higher incidence of AF in patients with type 2 DM. In addition, a greater GV is independently associated with higher chances of cardiac and all-cause mortality. To our knowledge, this is the first cohort study to explore the association of long-term GV with the development of AF.

High GV has been proved to be associated with increased risk for cardiovascular events and poor prognosis. [19, 20] However, its impact on arrhythmia has been seldom studied. In a large Korea cohort of healthy population, the metabolic variability score composed of glucose level, blood pressure, total cholesterol level, and BMI showed a close association with the risk of AF, and the incidence was about 0.8 to 1.2 per 1000 person-year. [21] In our T2DM cohort, the overall incidence of AF was 21.31 per 1000 person-year, which was apparently much higher than the Asian healthy population without DM. The pathophysiology of AF development in DM has not been elaborately investigated. In a diabetic mice model, increased AF susceptibility was associated with reduced atrial conduction velocity, action potential duration prolongation, increased heterogeneity in repolarization, and increased interstitial atrial fibrosis. [22] In addition to blood sugar level, increased magnitude of GV may generate more reactive oxygen species than hyperglycemia alone. In diabetic rats, glucose fluctuations promote cardiac fibrosis by altering AKT signaling pathway and upregulate Txnlp and NADPH oxidase expression which produce more reactive oxygen species levels, thereby increasing the incidence of AF. [23, 24] Other than direct effect, high GV may contribute to cardiac autonomic neuropathy which has a strong influence on cardiac arrhythmias. [25]

The clinical meanings of the long-term and short-term GVs are different. Long-term GV is derived based on visit-to-visit measurements of HbA1c and FG and is a marker of ambient hyperglycemia. In contrast, short-term GV represents episodes of either hyperglycemia or hypoglycemia within days. [26] In our study, we observed that HVS derived from HbA1c has better consistency and performance than FGCV derived from FG in predicting future events. This implies that the impact of GV on AF development is a long-term cumulative process.

Long-term visit-to-visit HbA1c variability has been proved to be a strong predictor for both microvascular and macrovascular diseases and also for all-cause mortality. [27, 28] There are several ways to evaluate the HbA1c variability. One study showed that among the HbA1c variability parameters including mean of HbA1c, yearly mean HbA1c, HbA1c-SD, HbA1c-CV and HVS, HVS performed the best in predicting microvascular events. [29] One reason is that many of the HbA1c variability parameters are affected by the mean HbA1c value. For example, since the mean HbA1c is the denominator of the CV, intensive DM treatment may lower the mean value while increase this variability index. [30] HVS is defined as a percentage of HbA1c fluctuation events and is relatively insensitive to the change of the HbA1c absolute value and thus can independently provide accurate and stable GV information. [18] Our study also identified some patient characteristics that are subjective to high GV including

male gender, high BMI, high baseline HbA1c and CKD. These factors could be an important reference for physicians who take care of patients with DM.

Limitations

First, we did not test all the reported GV parameters, such as average successive variability, average real variability of FG, mean amplitude of glycemic excursion. We chose FGCV and HVS since they were commonly used, easily calculated parameters that could help physicians quickly determine the GV of their patients. Second, we excluded patients with severe end-organ damage including CHF and CKD to avoid complex AF confounders existing in these medical conditions. Whether the conclusion can be extrapolated to these conditions need further confirmation. Third, we excluded subjects who were not consistently followed at our out-patient clinics since the outcomes might be missing. This approach might cause selection bias but it could make sure that all the outcomes were accurately determined. Finally, this was a retrospective cohort study and the causal relationship might be less convincing.

Conclusions

We conclude that high GV is independently associated with the development of new-onset AF in patients with T2DM. Reducing GV may be a potential new therapeutic target to prevent AF development.

Abbreviations

FGCV, coefficients of variability of fasting glucose; HVS, HbA1c variability score; BMI body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; PAOD, peripheral arterial occlusive disease; FG, fasting glucose; eGFR, estimated glomerular filtration rate; UCG, ultrasound cardiogram; LA, left atrium; DT, deceleration time; E/A:early diastolic transmitral flow velocity/ late diastolic transmitral flow velocity; E', early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; LVIDD, left ventricle internal end-diastolic diameter; LVEDD, left ventricle external end-diastolic diameter; LV mass, left ventricle mass; TRPG:tricuspid regurgitation pressure gradient; 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 2

Adjusted hazard ratios for AF, TIA/ischemic stroke, cardiac mortality and total mortality across quartiles of glycemic variability

Declarations

Ethics approval and consent to participate

The study protocol complies with the Declaration of Helsinki and was

approved by the Institutional Review Board of National Taiwan University Hospital.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used in this study were only available in the National Taiwan University Hospital. The SAS programs (codes) involved for this study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

LY-L contributed to the conception or design of the work. YY-Y and SL-C contributed to the acquisition, analysis of data for the work. JC-H interpreted and drafted the manuscript. CC-Y and LY-L critically revised the manuscript. All gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

Acknowledgements

The authors would like to express their thanks to the staff of Department of Medical Research for providing clinical data from National Taiwan University Hospital-integrated Medical Database (NTUH-iMD).

References

1. Ahmadi SS, Svensson A-M, Pivodic A, et al. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. *Cardiovasc Diabetol*. 2020 Jan 18;19(1):9.
2. Aune D, Feng T, Schlesinger S, et al. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: a systematic review and meta-analysis of cohort studies. *J Diabet Complicat*. 2018;32(5):501–11.
3. Hailey JJansen, Loryn JBohne, Anne MGillis, et al. Atrial remodeling and atrial fibrillation in acquired forms of cardiovascular disease. *Heart Rhythm*. 2020;1:147–59.
4. Keiichi Torimoto Y, Okada H, Mori Y, Tanaka. Relationship between fluctuations in glucose levels measured by continuous glucose monitoring and vascular endothelial dysfunction in type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2013 Jan;2:12:1.
5. Yoshifumi Saisho. Glycemic variability and oxidative stress: a link between diabetes and cardiovascular disease? *Int J Mol Sci*. 2014 Oct 13;15(10):18381–406.
6. Louis Monnier E, Mas C, Ginet, et al. Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA*. 2006 Apr;295(14):1681–7.
7. Jun JE, Jin S-M, Baek J, et al. The association between glycemic variability and diabetic cardiovascular autonomic neuropathy in patients with type 2 diabetes. *Cardiovasc Diabetol*. 2015 Jun 4;14:70.
8. Paolo Gesele G, Guglielmini M, De Angelis, et al. Acute, short-term hyperglycemia enhances shear stress-induced platelet activation in patients with type II diabetes mellitus. *J Am Coll Cardiol*. 2003 Mar;41(6):1013–20.
9. Zhaokun Pu L, Lai X, Yang, et al. Acute glycemic variability on admission predicts the prognosis in hospitalized patients with coronary artery disease: a meta-analysis. *Endocrine*. 2020 Mar;67(3):526–34.
10. Kozo Okada K, Hibi M, Gohbara, et al. Association between blood glucose variability and coronary plaque instability in patients with acute coronary syndromes. *Cardiovasc Diabetol*. 2015 Aug;20:14:111.
11. Guillaume Besch S, Pili-Floury C, Morel, et al. Impact of post-procedural glycemic variability on cardiovascular morbidity and mortality after transcatheter aortic valve implantation: a post hoc cohort analysis. *Cardiovasc Diabetol*. 2019 Mar;18(1):27.
12. Tao Zhang G, Su S-H, Mi, et al. Association Between Blood Glucose Variability and the Characteristics of Vulnerable Plaque in Elderly Non-ST Segment Elevation Acute Coronary Syndrome Patients. *Int Heart J*. 2019 May 30;60(3):569–576.
13. Weijing Feng Z, Li W, Guo, et al. Association Between Fasting Glucose Variability in Young Adulthood and the Progression of Coronary Artery Calcification in Middle Age. *Diabetes Care*. 2020 Oct;43(10):2574–80.
14. Shun Yokota H, Tanaka Y, Mochizuki, et al. Association of glycemic variability with left ventricular diastolic function in type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2019 Dec 5;18(1):166.
15. Justin B, Echouffo-Tcheugui S, Zhao G, Brock, et al. Visit-to-Visit Glycemic Variability and Risks of Cardiovascular Events and All-Cause Mortality: The ALLHAT Study. *Diabetes Care*. 2019 Mar;42(3):486–93.
16. Matthew W, Segar KV, Patel M, Vaduganathan, et al. Association of Long-term Change and Variability in Glycemia With Risk of Incident Heart Failure Among Patients With Type 2 Diabetes: A Secondary Analysis of the ACCORD Trial. *Diabetes Care*. 2020 Aug;43(8):1920–8.
17. Bancks MP, Carnethon MR, Jacobs DR Jr, et al. Fasting Glucose Variability in Young Adulthood and Cognitive Function in Middle Age: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Diabetes Care*. 2018 Dec;41(12):2579–85.
18. Li S, Nemeth I, Donnelly L, et al. Visit-to-Visit HbA_{1c} Variability Is Associated With Cardiovascular Disease and Microvascular Complications in Patients With Newly Diagnosed Type 2 Diabetes. *Diabetes Care*. 2020 Feb;43(2):426–32.
19. Yoichiro Hirakawa H, Arima S, Zoungas, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes Care*. 2014 Aug;37(8):2359–65.
20. Cardoso CRL, Leite NC, Moram CBM, et al. Long-term visit-to-visit glycemic variability as predictor of micro- and macrovascular complications in patients with type 2 diabetes: The Rio de Janeiro Type 2 Diabetes Cohort Study. *Cardiovasc Diabetol*. 2018 Feb 24;17(1):33.
21. Lee S-R, Choi E-K, Han K-D, et al. Effect of the variability of blood pressure, glucose level, total cholesterol level, and body mass index on the risk of atrial fibrillation in a healthy population. *Heart Rhythm*. 2020 Jan;17(1):12–9.
22. Loryn J, Bohne HJ, Jansen I, Daniel, et al. Electrical and structural remodeling contribute to atrial fibrillation in type 2 diabetic db/db mice. *Heart Rhythm*. 2021 Jan;18(1):118–29.
23. Shotaro Saito Y, Teshima A, Fukui, et al. Glucose fluctuations increase the incidence of atrial fibrillation in diabetic rats. *Cardiovasc Res*. 2014 Oct 1;104(1):5–14.

24. Changjiang Ying T, Liu H, Ling, et al. Glucose variability aggravates cardiac fibrosis by altering AKT signalling path. *Diab Vasc Dis Res.* 2017 Jul;14(4):327–335.
25. Ramya Ravi V, Balasubramaniam G, Kuppusamy, et al. Current concepts and clinical importance of glycemic variability. *Diabetes Metab Syndr* Mar-Apr. 2021;15(2):627–36.
26. Antonio Ceriello L, Monnier D, Owens. Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol.* 2019 Mar;7(3):221–30.
27. Sheng C-S, Tian J, Miao Y, et al. Prognostic Significance of Long-term HbA 1c Variability for All-Cause Mortality in the ACCORD Trial. *Diabetes Care.* 2020 Jun;43(6):1185–90.
28. Jang J-Y, Moon S, Cho S, et al. Visit-to-visit HbA1c and glucose variability and the risks of macrovascular and microvascular events in the general population. *Sci Rep.* 2019 Feb;4(1):1374. 9(.
29. Yang C-Y, Su P-F, Hung J-Y, et al. Comparative predictive ability of visit-to-visit HbA1c variability measures for microvascular disease risk in type 2 diabetes. *Cardiovasc Diabetol.* 2020 Jul 6;19(1):105.
30. Noyes JD, Soto-Pedre E, Donnelly LA, et al. Characteristics of people with high visit-to-visit glycaemic variability in Type 2 diabetes. *Diabet Med.* 2018 Feb;35(2):262–9.

Tables

Table 1: Baseline patients’ characteristics (N=27246)

	FGCV					HVS				
	Q1 (0.34-11.69)	Q2 (11.70-17.59)	Q3 (17.60-26.19)	Q4 (26.20-188.12)	P value	Q1 (1.37-18.17)	Q2 (18.18-33.99)	Q3 (34.00-51.10)	Q4 (51.11-100.00)	P value
N	6726 (24.69)	7099 (26.06)	6641 (24.37)	6780 (24.88)		6778 (24.88)	7855 (28.83)	6396 (23.48)	6217 (22.82)	
Age, mean (SD)	66.49 (9.38)	66.45 (9.51)	66.67 (9.75)	67.08 (10.14)	<0.001	66.59 (9.27)	66.76 (9.63)	66.73 (9.95)	66.58 (9.97)	0.598
Male (%)	3576 (53.17)	3808 (53.64)	3446 (51.89)	3672 (54.16)	0.054	3457 (51.00)	4167 (53.05)	3432 (53.66)	3446 (55.43)	<0.001
Baseline BMI, mean (SD)	25.70 (4.00)	25.82 (3.94)	25.87 (4.47)	25.52 (4.37)	<0.001	25.57 (3.90)	25.78 (4.04)	25.92 (4.57)	25.63 (4.29)	<0.001
Hypertension (%)	1188 (17.66)	1014 (14.28)	795 (11.97)	689 (10.16)	<0.001	1114 (16.44)	1129 (14.37)	779 (12.18)	664 (10.68)	<0.001
COPD (%)	102 (1.52)	83 (1.17)	70 (1.05)	88 (1.30)	0.094	85 (1.25)	101 (1.29)	81 (1.27)	76 (1.22)	0.990
CAD (%)	498 (7.40)	439 (6.18)	396 (5.96)	352 (5.19)	<0.001	413 (6.09)	506 (6.44)	382 (5.97)	384 (6.18)	0.685
PAOD (%)	51 (0.76)	41 (0.58)	61 (0.92)	72 (1.06)	0.011	47 (0.69)	74 (0.94)	57 (0.89)	47 (0.76)	0.327
History of TIA/stroke (%)	52 (0.77)	52 (0.73)	68 (1.02)	62 (0.91)	0.232	47 (0.69)	62 (0.79)	71 (1.11)	54 (0.87)	0.061
Baseline FG, mean (SD)	127.75 (25.14)	136.41 (32.37)	146.04 (45.97)	165.60 (86.89)	<0.001	128.06 (30.78)	138.59 (43.06)	149.87 (61.03)	161.69 (73.27)	<0.001
Baseline HbA1c, mean (SD)	6.94 (1.06)	7.22 (1.16)	7.64 (1.46)	8.21 (1.83)	<0.001	6.83 (0.95)	7.30 (1.26)	7.71 (1.47)	8.24 (1.82)	<0.001
Baseline eGFR, mean (SD)	77.85 (28.76)	75.73 (28.92)	72.52 (31.89)	64.96 (34.48)	<0.001	74.42 (28.04)	73.54 (30.63)	71.44 (32.36)	71.36 (34.87)	<0.001
CHA2DS2-VASc score, mean (SD)	0.49 (1.10)	2.44 (1.09)	2.46 (1.12)	2.45 (1.13)	0.042	2.49 (1.09)	2.48 (1.11)	2.45 (1.14)	2.40 (1.11)	<0.001
UCG										
LA size, mean (SD)	3.89 (0.67)	3.91 (0.65)	3.90 (0.65)	3.93 (0.68)	0.139	3.91 (0.63)	3.92 (0.66)	3.91 (0.66)	3.90 (0.69)	0.733
DT, mean (SD)	0.22(0.07)	0.23 (0.06)	0.23 (0.06)	0.22 (0.07)	<0.001	0.23 (0.06)	0.22 (0.06)	0.22 (0.07)	0.22 (0.07)	<0.001
E/A, mean (SD)	0.84 (0.39)	0.91 (3.30)	0.84 (0.49)	0.94 (3.12)	0.360	0.82 (0.37)	0.85 (0.56)	0.98 (4.52)	0.88 (1.04)	0.157
E/E', mean (SD)	26.72 (173.99)	17.17 (68.09)	18.21 (80.74)	22.49 (120.79)	0.675	30.50 (175.67)	15.26 (52.97)	24.00 (129.85)	19.58 (109.46)	0.369
LVEF, mean (SD)	118.08 (720.58)	109.55 (664.17)	119.60 (740.14)	118.29 (743.21)	0.964	133.56 (814.77)	117.11 (720.43)	100.62 (608.09)	117.04 (733.72)	0.506
LVIDD, mean (SD)	2.99 (0.66)	3.01 (0.67)	3.03 (0.66)	3.09 (0.74)	<0.001	2.96 (0.62)	3.03 (0.67)	3.07 (0.71)	3.08 (0.73)	<0.001
LVEDD, mean (SD)	4.76 (0.60)	4.78 (0.59)	4.78 (0.59)	4.77 (0.65)	0.825	4.78 (0.56)	4.78 (0.60)	4.78 (0.62)	4.75 (0.65)	0.304
LV mass, mean (SD)	199.69 (59.25)	201.15(59.57)	204.25 (57.80)	208.61 (64.07)	<0.001	200.24 (57.41)	201.81 (57.87)	206.87 (62.90)	206.12 (63.46)	<0.001
TRPG, mean (SD)	252.82 (46.28)	252.82(46.37)	252.85 (48.64)	257.39 (52.05)	<0.001	255.17 (44.75)	253.30 (47.15)	253.27 (49.34)	255.24 (52.92)	0.317
E, mean(SD)	77.62 (24.73)	78.97(25.02)	80.50 (26.83)	84.70 (29.17)	<0.001	78.69 (24.39)	80.51 (26.24)	81.22 (27.69)	82.42 (28.55)	<0.001
A, mean(SD)	95.13	97.18 (23.29)	98.73	100.54	<0.001	97.40	97.64	98.36	98.93	0.174

	(22.88)		(24.30)	(26.25)		(22.60)	(24.94)	(24.13)	(25.69)	
Medication										
Antiplatelet (%)	2706 (40.23)	3098 (43.64)	3028 (45.60)	3236 (47.73)	<0.001	2724 (40.19)	3457 (44.01)	3022 (47.25)	2865 (46.08)	<0.001
Anticoagulant (%)	351 (5.22)	359 (5.06)	390 (5.87)	471 (6.95)	<0.001	339 (5.00)	447 (5.69)	396 (6.19)	389 (6.26)	0.006
CCB (%)	3510 (52.19)	3937 (55.46)	3856 (58.06)	4153 (61.25)	<0.001	3699 (54.57)	4435 (56.46)	3774 (59.01)	3548 (57.07)	<0.001
Beta-blocker (%)	2541 (37.78)	2760 (38.88)	2697 (40.61)	2983 (44.00)	<0.001	2610 (38.51)	3154 (40.15)	2678 (41.87)	2539 (40.84)	0.001
ACEI/ARB (%)	3956 (58.82)	4528 (63.78)	4364 (65.71)	4466 (65.87)	<0.001	4280 (63.15)	5049 (64.28)	4144 (64.79)	3841 (61.78)	0.002
Diuretics (%)	1673 (24.87)	1975 (27.82)	2246 (33.82)	3078 (45.40)	<0.001	1751 (25.83)	2451 (31.20)	2356 (36.84)	2414 (38.83)	<0.001
Statin (%)	3820 (56.79)	4210 (59.30)	3995 (60.16)	3888 (57.35)	<0.001	4096 (60.43)	4676 (59.53)	3777 (59.05)	3364 (54.11)	<0.001
Propafenone (%)	165 (2.45)	171 (2.41)	163 (2.45)	146 (2.15)	0.609	186 (2.74)	199 (2.53)	145 (2.27)	115 (1.85)	0.006
Amiodarone (%)	327 (4.86)	386 (5.44)	463 (6.97)	704 (10.38)	<0.001	348 (5.13)	494 (6.29)	490 (7.66)	548 (8.81)	<0.001
Insulin (%)	946 (14.06)	1446 (20.37)	2458 (37.01)	4257 (62.79)	<0.001	1049 (15.48)	2263 (28.81)	2700 (42.21)	3095 (49.78)	<0.001
Metformin (%)	5406 (80.37)	6081 (85.66)	5532 (83.30)	4994 (73.66)	<0.001	5698 (84.07)	6477 (82.46)	5134 (80.27)	4704 (75.66)	<0.001
SGLT-2 inhibitor (%)	808 (12.01)	1370 (19.30)	1461 (22.00)	1147 (16.92)	<0.001	858 (12.66)	1450 (18.46)	1326 (20.73)	1152 (18.53)	<0.001
DPP4 inhibitor (%)	2908 (43.24)	4225 (59.52)	4437 (66.81)	4758 (70.18)	<0.001	3172 (46.80)	4710 (59.96)	4310 (67.39)	4136 (66.53)	<0.001
Sulphonylurea (%)	2395 (35.61)	4416 (62.21)	4824 (72.64)	4684 (69.09)	<0.001	3174 (46.83)	4779 (60.84)	4236(66.23)	4130 (66.43)	<0.001
Novonorm (%)	354 (5.26)	664 (9.35)	876 (13.19)	1307 (19.28)	<0.001	513 (7.57)	857 (10.91)	867 (13.56)	964 (15.51)	<0.001
Acarbose (%)	703 (10.45)	1119 (15.76)	1378 (20.75)	1678 (24.75)	<0.001	863 (12.73)	1375 (17.50)	1367 (21.37)	1273 (20.48)	<0.001
TZD (%)	619 (9.20)	1303 (18.35)	1670 (25.15)	1722 (25.40)	<0.001	992 (14.64)	1494 (19.02)	1433 (22.40)	1395 (22.44)	<0.001
GLP-1 agonist (%)	37 (0.55)	132 (1.86)	261(3.93)	331 (4.88)	<0.001	90 (1.33)	175 (2.23)	252 (3.94)	244 (3.92)	<0.001

Abbreviations: FGCv, coefficients of variability of fasting glucose; HVS, HbA1c variability score; BMI: body mass index; COPD, chronic obstructive pulmonary disease; CAD, coronary artery disease; PAOD, peripheral arterial occlusive disease; FG, fasting glucose; eGFR, estimated glomerular filtration rate; UCG, ultrasound cardiogram; LA, left atrium; DT, deceleration time; E/A: early diastolic transmitral flow velocity/ late diastolic transmitral flow velocity; E', early diastolic mitral annular velocity; LVEF, left ventricular ejection fraction; LVIDD, left ventricle internal end-diastolic diameter; LVEDD, left ventricle external end-diastolic diameter; LV mass, left ventricle mass; TRPG: tricuspid regurgitation pressure gradient; 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 2: Adjusted hazard ratios for AF, TIA/ischemic stroke, cardiac mortality and total mortality across quartiles of glycemic variability

Outcome	Group	No.	Event (%)	Model 1		Model 2		Model 3		Model 4	
				HR (95% C.I.)	p	HR (95% C.I.)	p	HR (95% C.I.)	p	HR (95% C.I.)	p
AF	FGCV_Q1	6726	514 (7.64)	ref.		ref.		ref.		ref.	
	FGCV_Q2	7099	616 (8.68)	1.09 (0.97 - 1.23)	0.137	1.08 (0.96 - 1.22)	0.199	1.10 (0.96 - 1.27)	0.174	1.08 (0.93 - 1.24)	0.319
	FGCV_Q3	6641	643 (9.68)	1.24 (1.10 - 1.39)	<0.001	1.18 (1.04 - 1.33)	0.008	1.11 (0.97 - 1.28)	0.139	0.98 (0.85 - 1.14)	0.822
	FGCV_Q4	6780	989 (14.59)	2.00 (1.80 - 2.22)	<0.001	1.74 (1.55 - 1.96)	<0.001	1.47 (1.29 - 1.69)	<0.001	1.11 (0.96 - 1.29)	0.165
TIA / stroke	FGCV_Q1	6726	376 (5.59)	ref.		ref.		ref.		ref.	
	FGCV_Q2	7099	407 (5.73)	1.00 (0.87 - 1.15)	0.971	0.98 (0.85 - 1.14)	0.823	1.08 (0.87 - 1.34)	0.505	0.97 (0.78 - 1.21)	0.770
	FGCV_Q3	6641	453 (6.82)	1.21 (1.05 - 1.38)	0.007	1.06 (0.92 - 1.23)	0.402	1.11 (0.89 - 1.37)	0.353	0.92 (0.74 - 1.16)	0.496
	FGCV_Q4	6780	567 (8.36)	1.53 (1.34 - 1.74)	<0.001	1.34 (1.16 - 1.55)	<0.001	1.34 (1.08 - 1.65)	0.007	1.03 (0.82 - 1.29)	0.821
Mortality	FGCV_Q1	6726	522 (7.76)	ref.		ref.		ref.		ref.	
	FGCV_Q2	7099	615 (8.66)	1.03 (0.92 - 1.16)	0.592	1.03 (0.91 - 1.16)	0.649	1.05 (0.87 - 1.26)	0.623	0.95 (0.79 - 1.14)	0.594
	FGCV_Q3	6641	816 (12.29)	1.50 (1.34 - 1.67)	<0.001	1.43 (1.27 - 1.61)	<0.001	1.30 (1.09 - 1.55)	0.003	1.00 (0.84 - 1.20)	0.975
	FGCV_Q4	6780	1589 (23.44)	3.15 (2.85 - 3.48)	<0.001	2.70 (2.42 - 3.02)	<0.001	2.42 (2.05 - 2.84)	<0.001	1.34 (1.13 - 1.60)	<0.001
Cardiac mortality	FGCV_Q1	6726	92 (1.37)	ref.		ref.		ref.		ref.	
	FGCV_Q2	7099	111 (1.56)	1.05 (0.80 - 1.39)	0.714	1.02 (0.76 - 1.37)	0.901	1.03 (0.71 - 1.51)	0.870	0.99 (0.67 - 1.45)	0.946
	FGCV_Q3	6641	142 (2.14)	1.47 (1.13 - 1.91)	0.003	1.18 (0.89 - 1.58)	0.256	1.08 (0.75 - 1.56)	0.685	0.90 (0.61 - 1.32)	0.577
	FGCV_Q4	6780	270 (3.98)	3.04 (2.40 - 3.85)	<0.001	1.91 (1.45 - 2.51)	<0.001	1.67 (1.18 - 2.36)	0.004	1.08 (0.75 - 1.55)	0.687
Non-cardiac mortality	FGCV_Q1	6726	430 (6.39)	ref.		ref.		ref.		ref.	
	FGCV_Q2	7099	504 (7.10)	1.03 (0.90 - 1.17)	0.675	1.03 (0.90 - 1.18)	0.678	1.04 (0.85 - 1.28)	0.691	0.94 (0.76 - 1.16)	0.562
	FGCV_Q3	6641	674 (10.15)	1.50 (1.33 - 1.69)	<0.001	1.48 (1.30 - 1.68)	<0.001	1.37 (1.13 - 1.67)	0.002	1.04 (0.84 - 1.27)	0.742
	FGCV_Q4	6780	1319 (19.45)	3.17 (2.84 - 3.54)	<0.001	2.86 (2.53 - 3.23)	<0.001	2.68 (2.23 - 3.22)	<0.001	1.42 (1.17 - 1.72)	<0.001

Outcome	Group	No.	Event (%)	Model 1		Model 2		Model 3			Model 4	
				HR (95% C.I.)	p	HR (95% C.I.)	p	HR	95% C.I.	p	HR (95% C.I.)	p
AF	HVS_Q1	6778	518 (7.64)	ref.		ref.		ref.			ref.	
	HVS_Q2	7855	733 (9.33)	1.30 (1.16 - 1.45)	<0.001	1.29 (1.15 - 1.45)	<0.001	1.21 (1.06 - 1.39)		<0.001	1.08 (0.95 - 1.24)	0.242
	HVS_Q3	6396	732 (11.44)	1.64 (1.47 - 1.84)	<0.001	1.60 (1.42 - 1.80)	<0.001	1.36 (1.19 - 1.55)		<0.001	1.15 (1.00 - 1.32)	0.044
	HVS_Q4	6217	779 (12.53)	1.97 (1.76 - 2.20)	<0.001	1.99 (1.77 - 2.25)	<0.001	1.58 (1.37 - 1.81)		<0.001	1.29 (1.12 - 1.48)	<0.001
TIA / stroke	HVS_Q1	6778	363 (5.36)	ref.		ref.		ref.			ref.	
	HVS_Q2	7855	507 (6.45)	1.25 (1.09 - 1.43)	0.001	1.22 (1.06 - 1.40)	0.006	1.22 (0.99 - 1.50)		0.059	1.07 (0.87 - 1.31)	0.547
	HVS_Q3	6396	504 (7.88)	1.55 (1.35 - 1.77)	<0.001	1.42 (1.23 - 1.63)	<0.001	1.44 (1.17 - 1.76)		<0.001	1.21 (0.98 - 1.50)	0.083
	HVS_Q4	6217	429 (6.90)	1.42 (1.23 - 1.63)	<0.001	1.34 (1.15 - 1.56)	<0.001	1.22 (0.98 - 1.52)		0.079	1.00 (0.79 - 1.26)	0.989
Mortality	HVS_Q1	6778	396 (5.84)	ref.		ref.		ref.			ref.	
	HVS_Q2	7855	821 (10.45)	1.96 (1.74 - 2.21)	<0.001	1.86 (1.64 - 2.11)	<0.001	1.73 (1.45 - 2.06)		<0.001	1.40 (1.17 - 1.67)	<0.001
	HVS_Q3	6396	951 (14.87)	2.91 (2.58 - 3.27)	<0.001	2.71 (2.39 - 3.06)	<0.001	2.22 (1.87 - 2.64)		<0.001	1.66 (1.39 - 1.98)	<0.001
	HVS_Q4	6217	1,374 (22.10)	5.07 (4.53 - 5.67)	<0.001	4.77 (4.23 - 5.38)	<0.001	3.66 (3.08 - 4.34)		<0.001	2.44 (2.04 - 2.91)	<0.001
Cardiac mortality	HVS_Q1	6778	85 (1.25)	ref.		ref.		ref.			ref.	
	HVS_Q2	7855	153 (1.95)	1.71 (1.31 - 2.23)	<0.001	1.42 (1.08 - 1.89)	0.013	1.41 (1.01 - 1.97)		0.046	1.14 (0.81 - 1.61)	0.449
	HVS_Q3	6396	155 (2.42)	2.22 (1.70 - 2.89)	<0.001	1.70 (1.28 - 2.26)	<0.001	1.28 (0.90 - 1.81)		0.175	1.00 (0.70 - 1.44)	0.988
	HVS_Q4	6217	222 (3.57)	3.87 (3.01 - 4.96)	<0.001	2.85 (2.16 - 3.76)	<0.001	2.08 (1.47 - 2.92)		<0.001	1.48 (1.04 - 2.10)	0.028
Non-cardiac mortality	HVS_Q1	6778	311 (4.59)	ref.		ref.		ref.			ref.	
	HVS_Q2	7855	668 (8.50)	2.03 (1.78 - 2.32)	<0.001	1.97 (1.71 - 2.26)	<0.001	1.85 (1.51 - 2.27)		<0.001	1.49 (1.21 - 1.83)	<0.001
	HVS_Q3	6396	796 (12.45)	3.09 (2.71 - 3.53)	<0.001	2.97 (2.59 - 3.40)	<0.001	2.62 (2.14 - 3.20)		<0.001	1.93 (1.57 - 2.37)	<0.001
	HVS_Q4	6217	1,152 (18.53)	5.40 (4.76 - 6.12)	<0.001	5.27 (4.61 - 6.03)	<0.001	4.34 (3.55 - 5.30)		<0.001	2.83 (2.31 - 3.47)	<0.001

Model 1: no adjustment. Model 2: adjusted for age, gender, baseline BMI, HTN, COPD, CAD, PAOD, history of TIA/ischemic stroke, baseline FG, baseline HbA1C, baseline eGFR; Model 3: adjusted for model2 plus UCG (LA size-LVEF-LV mass); Model 4: adjusted for model3 plus medications

Abbreviations as Table 1

Figures

Figure 1
Flow chart of patient selection

Figure 2

Forest plot of different outcomes in fully adjusted model stratified by quartiles of FGCV (2A) or HVS (2B).

Figure 3

Kaplan-Meier analysis stratified by HVS for different outcomes: AF (3a), total death (3b), cardiac death (3c) or non-cardiac death(3d)