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Visit-to-visit HbA1c variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes

Running Title: HbA1c variability and complications in diabetes

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Abstract

Objective: To investigate the association between visit-to-visit HbA1c variability and cardiovascular events and microvascular complications in patients with newly diagnosed type 2 diabetes.

Research Design and Methods: This retrospective cohort study analyzed patients from Tayside and Fife in the Scottish Care Information-Diabetes Collaboration (SCI-DC), who were observable from the diagnosis of diabetes and had at least five HbA1c measurements before the outcomes being evaluated. We used the previously reported HbA1c variability score (HVS) calculated as the percentage of the number of changes in HbA1c over 0.5% (5.5 mmol/mol) among all HbA1c measurement within an individual. The association between HVS and ten outcomes was assessed using Cox proportional-hazards models.

Results: We included 13,111 to 19,883 patients in the analyses of each outcome. The patients with HVS over 60% were associated with elevated risks of all outcomes compared with the lowest quintile (for example, hazard ratios and 95% confidence intervals [HVS >80 to ≤ 100 vs. HVS ≥ 0 to ≤ 20]: 2.38 [1.61~3.53] for major adverse cardiovascular events [MACE]; 2.4 [1.72~3.33] for all-cause mortality; 2.4 [1.13~5.11] for atherosclerotic cardiovascular [ASCV] death; 2.63 [1.81~3.84] for coronary artery disease; 2.04 [1.12~3.73] for ischemic stroke; 3.23 [1.76~5.93] for heart failure; 7.4 [3.84~14.27] for diabetic retinopathy; 3.07 [2.23~4.22] for diabetic peripheral neuropathy; 5.24 [2.61~10.49] for diabetic foot ulcer; 3.49 [2.47~4.95] for the newonset chronic kidney disease). Four sensitivity analyses, including adjustment for time-weighted average HbA1c confirmed the robustness of the results.

Conclusions: Our study shows that higher HbA1c variability is associated with increased risks of all-cause mortality, cardiovascular events and microvascular complication of diabetes independently of high HbA1c.

Keywords: HbA1c variability, cardiovascular event, all-cause mortality, heart failure, diabetic retinopathy, diabetic peripheral neuropathy, diabetic foot ulcer, chronic kidney disease

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Introduction

Although there is considerable evidence that intensive blood glucose normalization reduces the risk of both cardiovascular events and microvascular complications of diabetes (1-3), the effects were heterogeneous between trials. For example, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was terminated prematurely due to significantly elevated mortality and cardiovascular events (4), suggesting that the near-normalization of blood glucose should not be the only target of diabetes treatment. Glycemic variability is one factor that may explain these differences in cardiovascular outcomes.

Glycemic variability can be measured as either the glucose fluctuation within a day or the long-term visit-to-visit variability. The latter has been recently investigated in several studies, although the metrics and definition of the variability measure were inconsistent (5). Most studies evaluating HbA1c variability using the standard deviation (SD) or the coefficient of variation (CV) of HbA1c, suggested that these measures were associated with all-cause mortality and the development of the adverse outcomes of diabetes, after adjusting for the average HbA1c (6-11). However, neither SD or CV of HbA1c can be easily interpreted in clinical practice. Recently, Forbes and colleagues (12) developed a new scale, namely the HbA1c variability score (HVS) in the current study, to define the HbA1c variability. The HVS indicates how frequently the HbA1c rises or decreases by more than 0.5% (5.5mmol/mol), which is in line with the SD and CV of HbA1c but clinically more translatable (as it can be interpreted as the percentage of total HbA1c measures that vary by more than 0.5% or 5.5mmol/mol) (6,12). However, the HVS has not been widely used among the studies of HbA1c variability, with previous studies using this scale only focusing on the elderly and non-diabetic population and evaluating mainly mortality as an outcome (6,12). It is unclear whether HVS is associated with microvascular complications of diabetes and whether the increased cardiovascular risk described could be extended to real-world patients with type 2 diabetes. In this study we aimed to investigate the association between visit-to-

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visit HbA1c variability and both cardiovascular diseases and microvascular complications in a large population database of patients with newly diagnosed type 2 diabetes.

Research Design and Methods

Data source and study population

The population was selected from patients from Tayside and Fife in the Scottish Care Information-Diabetes Collaboration (SCI-DC), the electronic health record system used in Scotland for patients with diabetes. The patients were included if they: 1) were diagnosed with type 2 diabetes; 2) had their first HbA1c measurement within one year from diagnosis of diabetes; 3) were over 40 years old when first diagnosed with diabetes; 4) did not experience any study outcome before or within three years since diagnosis of diabetes; 5) had at least five records of HbA1c measurement between diagnosis of diabetes and the first episode of the study outcome. Patients were excluded where data were incomplete (details see the **Supplementary Techniques**). Data provision and linkage were carried by the University of Dundee Health Informatics Centre (HIC, https://www.dundee.ac.uk/hic), with analyses of anonymized data performed in an ISO27001 and Scottish Government accredited secure safe haven. HIC Standard Operating Procedures have been reviewed and approved by the NHS East of Scotland Research Ethics Service and consent for this study was obtained from the NHS Fife Caldicott Guardian.

Baseline parameters and follow-up

The body mass index (BMI), estimated glomerular filtration rate (eGFR), smoking status at baseline were captured from the medical record within one year from the diagnosis of diabetes (details see the **Supplementary Techniques**). The follow-up was defined by the first event of outcome or the last measurement of HbA1c before 24 April 2017 in the event-free case. Charlson Co-morbidity Index (CCI) was calculated using

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the ICD (International Classification of Diseases)-9 and ICD-10 code within the year after the diagnosis of diabetes (13), while we specifically removed the items of diabetes and cardiovascular events, which were overlapping with our population or outcomes.

Assessment of visit-to-visit HbA1c variability

To avoid the interaction between the HbA1c variability parameter with the frequency of HbA1c measurement and to better fit clinical practice, the HbA1c variability was evaluated using HVS, which was adopted from a recent publication (12). Briefly, HVS is the number of measures within an individual where the HbA1c has changed by > 0.5% (5.5mmol/mol) from the value prior, as a percentage of the total number of HbA1c measures between the diagnosis of diabetes and the outcome of interest for that individual (**Fig. S1**). To avoid the impact of multiple HbA1c measures in a short space of time, we allocated one HbA1c measure for every three-month period, using the median of all the HbA1c measures within that time. The resulting variability measure is termed the binned HVS (b-HVS). We also calculated the time-weighted average HbA1c, which was calculated using the area under the curve (AUC) of HbA1c from the diagnosis of diabetes to the first event divided by the duration.

Outcomes

We examined ten outcomes of interest including: major adverse cardiovascular events (MACE); all-cause mortality; atherosclerotic cardiovascular death (ASCV death); hospitalization or death from coronary artery disease, ischemic stroke or heart failure; observable background diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN); diabetic foot ulcer (DFU); and the new onset of chronic kidney diseases (CKD). If the event of interest occurred within the first three years from the diagnosis of diabetes, the patient was excluded from the analysis of that outcome, to avoid the outcome occurring close to diagnosis before the HVS could be defined, when the outcome would be unlikely to be related to the HVS. For full definitions of the endpoints (see the **Supplementary Techniques**).

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Statistical Analyses

The categorical variables were described using frequency and percentage. The continuous variables were described using means and SDs if normally distributed or median interquartile range (IQR) if not. Cox proportional-hazards model was used to assess the association between the HbA1c variability and each of the outcomes. The association of the adverse outcome with the HVS categories (≥ 0 to ≤ 20 , ≥ 20 to ≤ 40 , ≥ 40 to ≤ 60 , > 60 to ≤ 80 , > 80, with the ≥ 0 to ≤ 20 as reference) were adjusted for sex, index age, calendar year, Scottish Index of Multiple Deprivation (SIMD) quintiles, ever smoking, hypertension at baseline, BMI at baseline, high-density lipoprotein (HDL) cholesterol at baseline, eGFR at baseline, antiplatelet therapy at baseline and CCI (≥1 vs 0). We used Survival::cox.zph Pack in R to test the proportional hazards assumption for Cox regression models (14) for all our models. We considered the proportional hazards assumptions to be violated if the global P-value lower than 0.01. Because of the violation of proportional hazards assumptions the stage of CKD (stage 1 or 2) at baseline rather than the eGFR at baseline was stratified in the analysis of the new onset of the CKD. Five subgroup analyses were introduced based on the age (<65 years vs \geq 65 years), sex, BMI at baseline (>30kg/m² vs \leq 30kg/m²), time-weighted mean HbA1c (>7% vs <27% or >53mmol/mol vs <53mmol/mol), and treatment at baseline (medication/insulin-treated vs. lifestyle intervention only). Five sensitivity analyses were performed for each outcome by: 1) adjusting for time-weighted average HbA1c; 2) using the b-HVS instead of HVS; 3) using the HVS based on the HbA1c measurement solely focusing on the first three years after diagnosis of diabetes, prior to the occurrence of any event; 4) using the individual-level SDs of the HbA1c instead of the HVS; 5) using individual-level CVs of HbA1c instead of the HVS. Analyses were undertaken in the SAS® 9.4 (SAS Institute Inc., Cary, NC, USA). and the RStudio for Windows (R version 3.2.5).

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Results

Baseline characteristics

As shown in **Fig. 1**, among the 79,569 patients with type 2 diabetes identified in the population, we included 21,352 patients for further analysis., The average age was 63.3 \pm 11.1 years when recruited and 54.6% of them were male. The median follow-up duration was 6.8 (IQR: 4.6~11.2) years. The mean HbA1c at baseline was 7.7% \pm 2.0% (60.7 \pm 21.4 mmol/mol), and the median number of HbA1c measurements throughout the study period was 12 (IQR: 8~19) times during the follow-up duration. **Tab. S1** shows the baseline patient characteristics for those included for each analysis of outcomes and **Tab. 1** shows how the baseline characteristics differ across the HVS categories. 62% of the patients have an HVS below or equal to 40%; 12.5% have an HVS greater than 60%. As expected, an increasing HVS is associated with younger age of diagnosis, higher BMI, and more intensive diabetes treatment including greater insulin use.

HbA1c variability and outcomes

As shown in **Fig. 2**, between 13,111 to 19,883 patients were involved in the analyses of each outcome. Comparing with the reference (lowest HVS category, ≥ 0 to ≤ 20), patients with HVS over 60 were associated with increased risks of all outcomes in a fully adjusted Cox model. For example, those with HVS >80 to ≤ 100 had an increased risk of (HR [95%CI]): MACE: 2.38 [1.61~3.53]; all-cause mortality: 2.4 [1.72~3.33]; ASCV death: 2.4 [1.13~5.11]; coronary artery disease: 2.63 [1.81~3.84]; ischemic stroke: 2.04 [1.12~3.73]; heart failure: 3.23 [1.76~5.93]; DR: 7.4 [3.84~14.27]; DPN: 3.07 [2.23~4.22]; DFU: 5.24 [2.61~10.49]; CKD: 3.49 [2.47~4.95]).

Subgroup analyses and sensitivity analyses

Given the association between HVS and HbA1c we first undertook a sensitivity analysis, including time-weighted average HbA1c from diagnosis to event in the models (Fig. 3). The results were similar for most outcomes other than retinopathy where the

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association of HVS was diminished when adjusting for the time-weighted average HbA1c.

When comparing the subgroups with time-weighted average HBA1c more than or less than 7% (53mmol/mol) there was a stronger association between the HVS and coronary artery disease, ischemic stroke and progression to CKD in patients with time-weighted average HbA1c<7% or 53mmol/mol (Fig. S5). Other subgroup analyses were undertaken based on age (Fig. S2), sex (Fig. S3), obesity at baseline (Fig. S4) and treatment at baseline (Fig. S6) did not show significant differences in the trend of the association (except the cases with very small sample size). Using b-HVS instead of HVS also showed consistent results in all outcomes (Fig. S7). However, the sensitivity analysis using the first-three year HVS suggested a weaker association compared with the main analysis (Fig. S8). The sensitivity analysis using the individual-level SD (Fig. S9) and CV (Fig. S10) of HbA1c showed a similar pattern of risk for most outcomes but not ischemic stroke for SD and CV and diabetic retinopathy for CV where weaker associations were observed.

Discussion

To our knowledge, this is the first population-based study to investigate the association between the visit-to-visit HbA1c variability and comprehensive endpoints including cardiovascular events and the microvascular complications of diabetes in patients with newly diagnosed type 2 diabetes independent of the time-weighted average HbA1c.

Our study showed clear elevated risks of adverse events in the ~12.5% of patients with a HVS higher than 60 (meaning those with 60% of their HbA1c measurements increased or decreased by > 0.5% (5.5mmol/mol) compared with the last measurement) after diagnosis of diabetes adjusted for their time-weighted average HbA1c. The results were consistent with previous studies based on trial (15,16) and observational datasets (6-12,17). Our results indicate that frequent fluctuations of HbA1c of patients with

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diabetes may be an independent risk factor of poor prognosis and more stable HbA1c control may benefit the patients in clinical practice, although it should be emphasized that our results are observational and causal inference cannot be made. Of note, a recent analysis based on the VADT trial (16) suggested that higher HbA1c variability was associated with the increased risk of cardiovascular events in the group of intensive glycemic control but not the standard control. It suggested that the increased HbA1c variability may neutralize the cardiovascular benefits of the sustained 1.5% (16.4 mmol/mol) HbA1c reduction during the study period (18). We undertook a subgroup analysis looking at HVS in those with good and poor average HbA1c. It was interesting to note that the HVS association with atherosclerotic cardiovascular events was greater in those with good HbA1c, in keeping with the VADT finding. However, we need to interpret these results with caution as we can not account for treatment intensity during the study period.

We have previously reported that patients with high variability in HbA1c have high cardiovascular risk at baseline (19), and thus the association of HbA1c variability with risk may not be a feature of the HbA1c variability per se, but a marker of this baseline difference in patient characteristics. In this current study we have adjusted comprehensively for baseline differences in cardiovascular risk although we acknowledge there could be residual confounding. It is interesting to note that in the sensitivity analysis where we restrict our analysis to defining HbA1c variability only on the first three years of HbA1c measures, the association with micro- and macrovascular outcomes are diminished. This suggests that the HbA1c variability may continuously contribute to the clinical adverse endpoints beyond the first three years, and therefore that the risk can be less attributable to baseline differences in patient characteristics and more attributable to the HbA1c variability per se. As a recent study suggested that HbA1c variability is associated with the quality of patient care (20), it also suggests that it is never too late to reduce the HbA1c variability in clinical practice.

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Although infeasible in the current analysis, it would also be interesting to evaluate HbA1c variability on different anti-diabetic treatments to see if reduced variability can explain some of the improved outcomes with some of these agents.

Although we cannot attribute poor prognosis to the HbA1c variability per se, some underlying mechanisms may explain the association observed in our study. Although oxidative stress is suggested to be the explanation between short-term glycemic variability and adverse outcomes (5), it is not clear whether this is increased in patients with high visit-to-visit HbA1c variability. An alternative may relate to accumulated epigenetic modification induced by both high and low glycemia (21). Another explanation may simply relate to increased hypoglycemia in these individuals, since some studies suggest high HbA1c variability is linked to increased risk of severe hypoglycemic episodes (22) and patients admitted to hospital due to hypoglycemia have higher HbA1c variability (23). It will be valuable if a further study could address the frequency of overall and severe hypoglycemia among patients with different HbA1c variability.

The strengths of our study are clear. Firstly, all the included patients were tracked with their HbA1c measurement from the diagnosis of diabetes, so there is no period of the patients' diabetes journey that is not captured. Secondly, we comprehensively studied ten clinically important outcomes, including all-cause mortality, cardiovascular events and major microvascular complications of diabetes and showed consistent results across these micro- and macrovascular endpoints. Thirdly, our results were confirmed by a series of subgroup analyses and sensitivity analyses including adjusting for the time-weighted average HbA1c from the diagnosis of diabetes. Fourthly, our study was based on the real-world data of diabetes care in Scotland making these results directly translatable to clinical practice. Finally, we have used the HVS rather than SD or CV which we feel is much more clinically tractable. Although SD and CV reflect the dispersion trend of the HbA1c measures in an individual, they are no more than

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clinically meaningless statistical parameters. When considering the HVS, the clinicians can review the HbA1c profile for an individual – those where more than 60% of measures vary by more than 0.5% are at high risk.

The study does have limitations. Firstly, as a retrospective cohort study, uncorrected confounding could be possible and individuals with higher HbA1c variability may also at higher cardiovascular risks of other causes (18), and we cannot conclude an association of variability per se with the outcomes. Nevertheless, we used Cox proportional-hazards models to minimize the possible known confounding factors including CCI, smoking status and social deprivation and used a series of subgroup analyses and sensitivity analyses to confirm our findings to be robust. Secondly, we did not adjust for or evaluate the contribution of hypoglycemia, which has been reported to be associated with HbA1c variability (15) in the association between the HbA1c variability and outcomes because of the limitation of the data. Thirdly, the median follow-up duration of the study was 6.8 years and this will limit the total incident outcomes. The need to only include patients with newly diagnosed diabetes and other inclusion criteria do limit the total follow up time in this study population. This relatively short median duration does reduce the number of long-term outcome events especially for retinopathy and diabetic foot ulcer. Studies with longer follow-up duration in larger populations would be of value.

Conclusion

In conclusion, our study shows that higher HbA1c variability from the diagnosis of diabetes is independently associated with increased risks of all-cause mortality, major cardiovascular and microvascular complications of diabetes.

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Acknowledgment

SL, KZ and ERP conceived the study. SL, IN, LD and SH performed the statistical analyses. SL and ERP drafted the manuscript. ERP takes responsibility for the contents of the article as the guarantor.

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Conflict of interests: None to declare.

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Table and table legend

Table 1. Baseline characteristics of the overall study population

HVS Scores	≥0 to ≤20	>20 to ≤40	>40 to ≤60	>60 to ≤80	>80
n	7,084	6,096	5,502	2,409	261
Age of diabetes diagnosis, yrs	67.1 ± 10.3	63.5 ± 10.5	60.5 ± 10.9	58.9 ± 11.2	57.5 ± 11.2
Sex (male), n (%)	3,569 (50.4)	3,305 (54.2)	3,179 (57.8)	1,446 (60.0)	165 (63.2)
SIMD quintile, n (%)					
Q1	1,251 (17.7)	1,165 (19.1)	1,171 (21.3)	503 (20.9)	62 (23.8)
Q2	1,263 (17.8)	1,134 (18.6)	1,121 (20.4)	471 (19.6)	51 (19.5)
Q3	1,328 (18.7)	1,175 (19.3)	1,016 (18.5)	493 (20.5)	52 (19.9)
Q4	1,936 (27.3)	1,629 (26.7)	1,409 (25.6)	634 (26.3)	60 (23.0)
Q5	1,306 (18.4)	993 (16.3)	785 (14.3)	308 (12.8)	36 (13.8)
Year of diabetes diagnosis [*]	2010 [2005,	2008 [2002,	2008 [2002,	2009 [2003,	2010 [2006,
	2012]	2011]	2011]	2011]	2013]
BMI, kg/m ²	31.3 ± 6.0	31.9 ± 6.2	32.8 ± 6.5	33.3 ± 7.1	33.2 ± 7.3
Ever smoking, n (%)	4,881 (68.9)	4,336 (71.1)	3,977 (72.3)	1,748 (72.6)	178 (68.2)
Ever regular alcohol, n (%)	4,008 (61.2)	3,345 (59.1)	2,875 (57.3)	1,185 (54.5)	131 (56.5)
Systolic blood pressure, mmHg	140.1 ± 19.0	141.2 ± 19.5	140.3 ± 19.8	139.6 ± 19.6	138.2 ± 19.4
Diastolic blood pressure, mmHg	78.9 ± 10.8	81.0 ± 10.9	82.2 ± 11.2	82.2 ± 11.4	82.2 ± 12.0
Carlson Comorbidity Index ≥1, n (%)	1,332 (18.8)	1,073 (17.6)	867 (15.8)	449 (18.6)	58 (22.2)
Hypertension, n (%)	5,505 (77.7)	4,376 (71.8)	3,786 (68.8)	1,574 (65.3)	155 (59.4)
Treatment of diabetes within the first year from the					
diagnosis of diabetes, n (%)					
Lifestyle intervention only	5,260 (74.3)	3,137 (51.5)	2,190 (39.8)	740 (30.7)	61 (23.4)
Anti-diabetic agents without insulin	1,770 (25.0)	2,821 (46.3)	3,153 (57.3)	1,569 (65.1)	188 (72.0)

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Treated with insulin	54 (0.8)	138 (2.3)	159 (2.9)	100 (4.2)	12 (4.6)
Receiving anti-platelet therapy, n (%)	2,465 (34.8)	1,909 (31.3)	1,598 (29.0)	667 (27.7)	67 (25.7)
Receiving statins, n (%)	4,866 (68.7)	3,716 (61.0)	3,218 (58.5)	1,373 (57.0)	161 (61.7)
HbA1c at baseline, %	6.7 ± 1.2	7.8 ± 1.9	8.4 ± 2.1	8.9 ± 2.3	9.6 ± 2.5
HbA1c at baseline, mmol/mol	49 ± 13.0	62 ± 20.3	68 ± 23.1	77.4 ± 24.6	81 ± 26.8
HDL cholesterol, mmol/L	1.3 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Non-HDL cholesterol, mmol/L	3.5 ± 1.2	3.8 ± 1.2	3.9 ± 1.3	4.0 ± 1.3	4.0 ± 1.1
ALT, IU/L*	24 [18, 34]	28 [20, 39]	30 [21, 45]	32 [22, 48]	32 [22, 48]
eGFR, mL/min/1.73m ²	72.2 ± 18.7	73.7 ± 18.8	77.2 ± 19.1	80.7 ± 19.7	84.1 ± 20.8

* Presented as median [the interquartile range]

Abbreviations: ALT: alanine aminotransferase; BMI: body mass index; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein;

SIMD: Scottish Index of Multiple Deprivation

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Figures and figure legends

Figure 1. The flow diagram of the patient selection

Abbreviations: ASCV: atherosclerotic cardiovascular; CKD: chronic kidney diseases; CV: cardiovascular; DFU: diabetic foot ulcer; DPN: diabetic peripheral neuropathy; DR: diabetic retinopathy; MACE: major adverse cardiovascular events.

Figure 2. The association between HbA1c variability score and adverse

outcomes in patients with newly diagnosed type 2 diabetes

Abbreviations: CI: confidence interval; HR: hazard ratio.

Figure 3. The association between HbA1c variability score and adverse

outcomes in patients with newly diagnosed type 2 diabetes after adjusting for the time-weighted average HbA1c

Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.

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Figure 1. The flow diagram of the patient selection

Abbreviations: ASCV: atherosclerotic cardiovascular; CKD: chronic kidney diseases; CV: cardiovascular; DFU: diabetic foot ulcer; DPN: diabetic peripheral neuropathy; DR: diabetic retinopathy; MACE: major adverse cardiovascular events.

195x211mm (150 x 150 DPI)

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 2389 N = 17366	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80	662 / 5693 714 / 5050 687 / 4510 300 / 1921	iei iei	1 (Ref) 0.99 (0.89 ~ 1.11) 1.28 (1.14 ~ 1.43) 1.89 (1.64 ~ 2.17)	0.907 <0.001 <0.001
All-cause mortality	>80 to <=100	26 / 192		2.38 (1.61 ~ 3.53)	<0.001
N = 19883	>20 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	1208 / 5779 1143 / 5160 497 / 2201 37 / 210		0.96 (0.88 ~ 1.04) 1.24 (1.14 ~ 1.35) 1.85 (1.66 ~ 2.06) 2.40 (1.72 ~ 3.33)	0.297 <0.001 <0.001 <0.001
Atherosclerotic cardiovascular death	1				
Event = 892 N = 19746	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	226 / 6468 289 / 5752 269 / 5133 101 / 2183 7 / 210	⊨-1 -=1 -=-1	1 (Ref) 1.12 (0.94 ~ 1.34) 1.37 (1.14 ~ 1.65) 1.82 (1.43 ~ 2.31) 2.40 (1.13 ~ 5.11)	0.204 0.001 <0.001 0.023
Coronary artery disease					
Event = 2228 N = 16413	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	603 / 5385 698 / 4781 622 / 4228 276 / 1830 29 / 189	• + -= -=-	1 (Ref) 1.03 (0.92 ~ 1.15) 1.17 (1.04 ~ 1.32) 1.67 (1.44 ~ 1.94) 2.63 (1.81 ~ 3.84)	0.595 0.008 <0.001 <0.001
Ischemic stroke					
Event = 1136 N = 18609	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	365 / 6085 321 / 5398 306 / 4851 133 / 2070 11 / 205		1 (Ref) 0.84 (0.72 ~ 0.98) 1.07 (0.91 ~ 1.25) 1.52 (1.24 ~ 1.86) 2.04 (1.12 ~ 3.73)	0.025 0.439 <0.001 0.020
Heart failure					
Event = 853 N = 19059	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	243 / 6286 257 / 5538 239 / 4932 103 / 2093 11 / 210		1 (Ref) 1.03 (0.86 ~ 1.23) 1.27 (1.05 ~ 1.53) 1.87 (1.48 ~ 2.37) 3.23 (1.76 ~ 5.93)	0.733 0.013 <0.001 <0.001
Diabetic retinopathy					
Event = 414 N = 15067	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	61 / 5079 108 / 4462 164 / 3752 70 / 1605 11 / 169		1 (Ref) 1.13 (0.82 ~ 1.56) 1.99 (1.47 ~ 2.70) 2.92 (2.05 ~ 4.17) 7.40 (3.84 ~ 14.27)	0.448 <0.001 <0.001 <0.001
Diabetic peripheral neuropathy					
Event = 2526 N = 13111	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	650 / 4351 799 / 3885 747 / 3312 289 / 1394 41 / 169	■ = =	1 (Ref) 1.13 (1.02 ~ 1.26) 1.35 (1.21 ~ 1.51) 1.59 (1.38 ~ 1.84) 3.07 (2.23 ~ 4.22)	0.020 <0.001 <0.001 <0.001
Diabetic foot ulcer					
Event = 468 N = 15913	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	87 / 5253 128 / 4731 171 / 4055 73 / 1694 9 / 180		1 (Ref) 1.24 (0.94 ~ 1.63) 2.06 (1.58 ~ 2.70) 3.01 (2.18 ~ 4.15) 5.24 (2.61 ~ 10.49)	0.134 <0.001 <0.001 <0.001
Chronic kidney disease					
Event = 1722 N = 13812	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	411 / 4160 554 / 3904 518 / 3809 204 / 1734 35 / 205		1 (Ref) 1.13 (0.99 ~ 1.28) 1.20 (1.05 ~ 1.38) 1.56 (1.31 ~ 1.85) 3.49 (2.47 ~ 4.95)	0.074 0.007 <0.001 <0.001
		0.	50 2.04.08.0		

Figure 2. The association between HbA1c variability score and adverse outcomes in patients with newly diagnosed type 2 diabetes Abbreviations: CI: confidence interval; HR: hazard ratio.

423x635mm (72 x 72 DPI)

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE					
Event = 2389	>=0 to <=20	662 / 5693	+	1 (Ref)	
N = 17366	>20 to <=40	714 / 5050	H=1	1.11 (0.98 ~ 1.25)	0.107
	>40 to <=60	687 / 4510	H	1.38 (1.20 ~ 1.60)	< 0.001
	>60 to <=80	300 / 1921	HEH	1.96 (1.64 ~ 2.35)	<0.001
	>80 to <=100	26 / 192	⊢ ∎−1	2.46 (1.63 ~ 3.72)	<0.001
All-cause mortality					
Event = 4090	>=0 to <=20	1205 / 6533		1 (Ref)	
N = 19883	>20 to <=40	1208 / 5779	IH .	1.17 (1.07 ~ 1.28)	0.001
	>40 to <=60	1143 / 5160	Hel	1.62 (1.45 ~ 1.80)	< 0.001
	>60 to <=80	497 / 2201	H=1	2.43 (2.11 ~ 2.78)	< 0.001
	>80 to <=100	37 / 210	H	3.15 (2.24 ~ 4.44)	<0.001
Atherosclerotic cardiovascular dea	th				
Event = 892	>=0 to <=20	226 / 6468	•	1 (Ref)	
N = 19746	>20 to <=40	289 / 5752	⊢ •-+	1.24 (1.01 ~ 1.52)	0.039
	>40 to <=60	269 / 5133	H=-1	1.47 (1.16 ~ 1.87)	0.001
	>60 to <=80	101 / 2183		1.85 (1.37 ~ 2.50)	<0.001
	>80 to <=100	7/210		2.46 (1.13 ~ 5.37)	0.024
Coronary artery disease					
Event = 2228	>=0 to <=20	603 / 5385	- +	1 (Ref)	
N = 16413	>20 to <=40	698 / 4781	H=H	1.15 (1.01 ~ 1.31)	0.034
	>40 to <=60	622 / 4228	HEH	1.26 (1.08 ~ 1.46)	0.003
	>60 to <=80	276 / 1830	H	1.70 (1.41 ~ 2.05)	<0.001
	>80 to <=100	29 / 189		2.66 (1.79 ~ 3.95)	<0.001
Ischemic stroke					
Event = 1136	>=0 to <=20	365 / 6085	•	1 (Ref)	
N = 18609	>20 to <=40	321 / 5398	H H 1	0.92 (0.78 ~ 1.10)	0.371
	>40 to <=60	306 / 4851		1.20 (0.98 ~ 1.48)	0.080
	>60 to <=80	133 / 2070	H=-1	1.72 (1.33 ~ 2.23)	<0.001
	>80 to <=100	11/205		2.30 (1.23 ~ 4.32)	0.009
Heart failure					
Event = 853	>=0 to <=20	243 / 6286	- +	1 (Ref)	
N = 19059	>20 to <=40	257 / 5538	H=-1	1.24 (1.01 ~ 1.51)	0.042
	>40 to <=60	239 / 4932	H=H	1.60 (1.25 ~ 2.03)	<0.001
	>60 to <=80	103/2093		2.35 (1.74 ~ 3.19) + 4 17 (2 19 ~ 7 93)	<0.001
Diabetic retinopathy	>=0 to <=20	61 / 5070		1 (Pof)	
Event - 414	>20 to <=20	109/4462	L.	0.99 (0.60 - 1.29)	0.406
N = 15007	>40 to <=60	164 / 3752		$1.03(0.69 \sim 1.28)$	0.490
	>60 to <=80	70 / 1605	· · · · · ·	1.00(0.00 - 1.04) 1.18(0.74 ~ 1.86)	0.490
	>80 to <=100	11 / 169	H	2.83 (1.38 ~ 5.83)	0.005
Dishetia againhard aguragathu					
Event = 2526	>=0 to <=20	650 / 4351	1	1 (Ref)	
N = 13111	>20 to <=40	799 / 3885	-	1.15 (1.02 ~ 1.30)	0.022
	>40 to <=60	747 / 3312	H=1	$1.24(1.08 \sim 1.43)$	0.003
	>60 to <=80	289 / 1394	H=4	1.36 (1.14 ~ 1.62)	0.001
	>80 to <=100	41 / 169	H=	2.59 (1.84 ~ 3.62)	<0.001
Diabetic foot ulcer					
Event = 468	>=0 to <=20	87 / 5253		1 (Ref)	
N = 15913	>20 to <=40	128 / 4731	—	1.34 (0.97 ~ 1.84)	0.074
	>40 to <=60	171 / 4055	H	1.90 (1.33 ~ 2.71)	< 0.001
	>60 to <=80	73 / 1694	⊢ ∎–1	2.42 (1.60 ~ 3.68)	< 0.001
	>80 to <=100	9 / 180		⊣ 4.14 (1.96 ~ 8.73)	< 0.001
Chronic kidney disease					
Event = 1722	>=0 to <=20	411/4160	- -	1 (Ref)	
N = 13812	>20 to <=40	554 / 3904	Hert	1.23 (1.07 ~ 1.42)	0.005
	>40 to <=60	518 / 3809	HH	1.33 (1.13 ~ 1.57)	0.001
	>60 to <=80	204 / 1734	H=	1.70 (1.37 ~ 2.10)	< 0.001
	>80 to <=100	35 / 205	H	3.85 (2.65 ~ 5.60)	< 0.001
				1	
		0	.501.0 2.0 4.0 8	.0	

Figure 3. The association between HbA1c variability score and adverse outcomes in patients with newly diagnosed type 2 diabetes after adjusting for the time-weighted average HbA1c Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.

423x635mm (72 x 72 DPI)

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Supplementary Techniques

Study exclusion criteria

They were excluded if they had: 1) unavailable data of sex, date of birth, Scottish Index of Multiple Deprivation (SIMD) or smoking records throughout the study period; 2) unavailable data of body mass index (BMI), serum creatinine or highdensity lipoprotein (HDL) cholesterol within a year since diagnosis of diabetes; 3) free of the record of Scottish diabetes routine check when analyzing the outcomes of diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN), diabetic foot ulcer (DFU); 5) with the estimated glomerular filtrate rate (eGFR) lower than 60 mL/min per 1.73m² at baseline when analyzing the outcome of new onset of chronic kidney diseases (CKD).

Defining the baseline characteristics

The patients were recognized to be ever smoking if there were any records of current or previous smoking in their the record in the electronic medical record (EMR) database. All baseline characteristics were using the data within a year since diagnosis of diabetes. BMI was extracted from the EMR database. The laboratory tests were extracted for the laboratory information systems. The eGFR was calculated using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation. Hypertension at baseline was identified if there were at least two episodes of elevated blood pressures in different days (systolic blood pressure >140mmHg or diatolic blood pressure >90mmHg), or receiving at least two prescriptions of the antihypertensive drug (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, beta-blockers or non-dihydroxypyridine calcium channel blockers). The baseline oral anti-diabetic agents (metformin, sulphonylureas, gliptins, acarbose, thiazolidinediones, dipeptidyl peptidase-4 inhibitors and sodium-glucose cotransporter-2 inhibitors), insulin, antiplatelet therapy and statins at baseline were identified if there were at least two prescriptions of the drug class within the first year of diagnosis. If the patients used insulin combined with oral agents, we considered insulin as a priority.

Defining the outcomes

All-cause mortality was identified as any death record in the General Registry Office or the Community Health Index (CHI) registry. Cardiovascular death was identified as the death due to ischemic stroke (defined as ICD-9: 433, 434, 435 or 436; ICD-10: I63, I64, I65 or I66) or coronary artery disease (defined as ICD-9: 410, 411, 412, 413 or 414; ICD-10: I20, I21, I22, I23, I24 or I25). The cardiovascular outcomes were identified if the patients were hospitalized or died due to the coronary artery disease, ischemic stroke or heart failure (defined as ICD-9: 428 or ICD10: I50), respectively. Major adverse cardiovascular events (MACE) was defined as a composite outcome of cardiovascular death, ischemic stroke and coronary artery diseases. DR was identified as the first episode of observable background or more advanced retinopathy according to the annual retinal photograph taken as part of the routine care or receiving a laser treatment based on the records in the Scottish Care Information-Diabetes Collaboration (SCI-DC). DPN and DFU were identified as the first episode of impaired monofilament test and the first record of active foot ulcer according to the record of the SCI-DC system as part of the routine care in Scotland, respectively. CKD was identified for the first episode of persistently reduced eGFR (all eGFR values in and between two nonadjacent months were below 60 mL/min per 1.73m²).

 Table S1. Baseline characteristics of patients for those included for each analysis of outcomes.

	MACE	All-cause	Cardiovascu	Coronary	Ischemic	Heart	Diabetic	Diabetic	Diabetic	Chronic
	(n =	mortality (n	lar death (n	artery disease	stroke (n	failure (n	retinopathy	peripheral	foot ulcer	kidney
	17,366)	= 19.883)	= 19,746)	(n = 16,413)	= 18,609)	= 19,059)	(n = 15,067)	neuropathy (n =	(n = 15,913)	disease (n =
								13,111)		13,812)
Age of diabetes diagnosis, yrs	62.7 ±	63.2 ± 11.0	63.1 ± 11.0	62.5 ± 11.0	62.9 ± 10.9	62.9 ±	62.8 ± 10.7	62.3 ± 10.6	63.0 ± 10.8	59.5 ± 9.8
	11.0					10.9				
Sex (male), n (%)	9,202	10,854	10,777 (54.6)	8,594 (52.4)	10,080	10,329	8,206 (54.5)	7,061 (53.9)	8,577 (53.9)	8,418 (60.9)
	(53.0)	(54.6)			(54.2)	(54.2)				
SIMD quintile, n (%)										
Q1	3,246	3,818 (19.2)	3,784 (19.2)	3,073 (18.7)	3,534	3,636	2,863 (19.0)	2,459 (18.8)	3,028 (19.0)	2,724 (19.7)
	(18.7)				(19.0)	(19.1)				
Q2	3,265	3,755 (18.9)	3,738 (18.9)	3,015 (18.4)	3,526	3,597	2,812 (18.7)	2,424 (18.5)	2,960 (18.6)	2,590 (18.8)
	(18.8)				(18.9)	(18.9)				
Q3	3,282	3,789 (19.1)	3,756 (19.0)	3,130 (19.1)	3,518	3,620	2,863 (19.0)	2,440 (18.6)	3,005 (18.9)	2,597 (18.8)
	(18.9)				(18.9)	(19.0)				
Q4	4,710	5,315 (26.7)	5,275 (26.7)	4,467 (27.2)	5,003	5,114	4,061 (27.0)	3,627 (27.7)	4,343 (27.3)	3,667 (26.5)
	(27.1)				(26.9)	(26.8)				
Q5	2,863	3,206 (16.1)	3,193 (16.2)	2,728 (16.6)	3,028	3,092	2,468 (16.4)	2,161 (16.5)	2,577 (16.2)	2,234 (16.2)
	(16.5)				(16.3)	(16.2)				
Year of diabetes diagnosis*	2009	2009 [2003,	2009 [2003,	2009 [2003,	2009	2009	2008 [2003,	2006 [2002,	2006 [2002,	2009 [2004,
	[2003,	2011]	2011]	2011]	[2003,	[2003,	2010]	2010]	2010]	2011]
	2011]				2011]	2011]				
BMI, kg/m ²	32.2 ±	32.1 ± 6.4	32.1 ± 6.4	32.2 ± 6.5	32.2 ± 6.4	32.1 ± 6.4	32.2 ± 6.3	32.0 ± 6.3	32.0 ± 6.3	32.6 ± 6.5
	6.4									

	10.000		4 4 6 4 6 (= 4 6)	11.010 ((0.0)	10.105	10.150	10 1			
Ever smoking, n (%)	12,065	14,122	14,019 (71.0)	11,310 (68.9)	13,125	13,452	10,774	9,402 (71.7)	11,421	9,790 (70.9)
	(69.5)	(71.0)			(70.5)	(70.6)	(71.5)		(71.8)	
Ever regular alcohol, n (%)	9,420	10,823	10,771 (58.8)	8,840 (58.3)	10,177	10,410	8,378 (59.0)	7,389 (59.6)	8,733 (58.3)	8,043 (63.0)
	(58.5)	(58.7)			(58.9)	(58.9)				
Systolic blood pressure,	141.1 ±	140.6 ± 19.5	140.6 ± 19.4	141.4 ± 19.3	140.7 ±	$140.8 \pm$	140.8 ± 19.2	141.4 ± 19.5	141.2 ± 19.6	139.9 ± 18.9
mmHg	19.3				19.3	19.3				
Diastolic blood pressure,	81.4 ±	80.9 ± 11.1	80.9 ± 11.0	81.7 ± 10.9	81.1 ± 11.0	81.1 ±	81.1 ± 10.9	81.5 ± 11.0	81.2 ± 11.0	82.0 ± 10.9
mmHg	10.9					11.0				
Carlson Comorbidity Index	2,599	3,369 (16.9)	3,328 (16.9)	2,326 (14.2)	2,952	3,064	2,364 (15.7)	1,829 (14.0)	2,424 (15.2)	1,867 (13.5)
≥1, n (%)	(15.0)				(15.9)	(16.1)				
Hypertension, n (%)	12,166	14,323	14,214 (72.0)	11,311 (68.9)	13,282	13,600	10,916	9,425 (71.9)	11,522	9,282 (67.2)
	(70.1)	(72.0)			(71.4)	(71.4)	(72.4)		(72.4)	
Treatment of diabetes within										
the first year from the										
diagnosis of diabetes, n (%)										
Lifestyle intervention only	9,259	10,685	10,618 (53.8)	8,662 (52.8)	9,951	10,255	8,175 (54.3)	7,116 (54.3)	8,601 (54.1)	7,034 (50.9)
	(53.3)	(53.7)			(53.5)	(53.8)				
Anti-diabetic agents without	7,789	8,791 (44.2)	8,727 (44.2)	7,443 (45.3)	8,279	8,430	6,585 (43.7)	5,724 (43.7)	6,990 (43.9)	6,522 (47.2)
insulin	(44.9)				(44.5)	(44.2)				
Treated with insulin	318	407 (2.0)	401 (2.0)	308 (1.9)	379 (2.0)	374 (2.0)	307 (2.0)	271 (2.1)	322 (2.0)	256 (1.9)
	(1.8)									
Receiving anti-platelet	4,510	6,232 (31.3)	6,170 (31.2)	3,832 (23.3)	5,459	5,769	4,790 (31.8)	4,049 (30.9)	5,052 (31.7)	3,555 (25.7)
therapy, n (%)	(26.0)				(29.3)	(30.3)				
Receiving statins, n (%)	10,385	12,333	12,252 (62.0)	9,592 (58.4)	11,391	11,743	9,238 (61.3)	7,680 (58.6)	9,513 (59.8)	8,472 (61.3)
	(59.8)	(62.0)			(61.2)	(61.6)				

HbA1c, %	7.7 ±	7.7 ± 2.0	7.7 ± 2.0	7.8 ± 2.0	7.7 ± 2.0	7.7 ± 2.0	7.7 ± 2.0	7.8 ± 2.0	7.8 ± 2.0	7.8 ± 2.0
	2.0									
HbA1c, mmol/mol	61 ±	61 ± 21.6	61 ± 21.5	61 ± 22.0	61 ± 21.6	61 ± 21.5	61 ± 21.5	61 ± 22.1	61 ± 21.9	62 ± 22.0
	21.8									
HDL cholesterol, mmol/L	1.2 ±	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
	0.3									
Non-HDL cholesterol,	3.9 ±	3.8 ± 1.3	3.8 ± 1.3	3.9 ± 1.2	3.8 ± 1.2	3.8 ± 1.3	3.8 ± 1.2	3.9 ± 1.3	3.9 ± 1.3	3.9 ± 1.3
mmol/L	1.2									
ALT, IU/L*	28 [20,	28 [20, 40]	28 [20, 40]	28 [20, 41]	28 [20, 41]	28 [20,	28 [20, 41]	28 [20, 41]	28 [20, 41]	30 [22, 44]
	41]					40]				
eGFR, mL/min/1.73m ²	75.5 ±	74.7 ± 19.0	74.8 ± 18.9	75.8 ± 18.8	75.1 ± 18.8	75.1 ±	73.3 ± 18.1	73.4 ± 17.8	73.1 ± 18.1	83.0 ± 14.5
	18.7					18.7				

* Presented as median [the interquartile range]

Abbreviations: ALT: alanine aminotransferase; BMI: body mass index; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein; SIMD: Scottish Index of Multiple Deprivation



Figure S1. The definition of HbA1c Variability Score (HVS)



Figure S2. The subgroup analysis based on the age

A.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 908 N = 9894	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	143 / 2393 252 / 2861 332 / 3084 162 / 1405 19 / 151		1 (Ref) 0.93 (0.76 ~ 1.15) 1.10 (0.90 ~ 1.35) 1.68 (1.33 ~ 2.11) 2.64 (1.63 ~ 4.27)	0.494 0.353 <0.001 <0.001
All-cause mortality Event = 1232 N = 10919	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	212 / 2643 335 / 3148 437 / 3402 227 / 1559 21 / 167	⊨= == -=-	1 (Ref) 0.80 (0.67 ~ 0.95) 0.95 (0.80 ~ 1.12) 1.58 (1.31 ~ 1.92) 2.18 (1.39 ~ 3.42)	0.010 0.546 <0.001 0.001
Atherosclerotic cardiovascular death Event = 298 N = 10897	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	39 / 2637 92 / 3145 108 / 3393 53 / 1556 6 / 166		1 (Ref) 1.11 (0.76 ~ 1.62) 1.14 (0.78 ~ 1.66) 1.90 (1.25 ~ 2.90) 3.78 (1.59 ~ 9.00)	0.586 0.496 0.003 0.003
Coronary artery disease Event = 969 N = 9461	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	177 / 2340 283 / 2729 328 / 2900 158 / 1343 23 / 149	++ ++ ++ -+-	1 (Ref) 0.88 (0.73 ~ 1.06) 0.90 (0.75 ~ 1.09) 1.31 (1.05 ~ 1.63) 2.39 (1.54 ~ 3.70)	0.188 0.277 0.018 <0.001
Ischemic stroke Event = 417 N = 10440	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	79 / 2506 113 / 3018 149 / 3262 67 / 1491 9 / 163		1 (Ref) 0.79 (0.59 ~ 1.06) 0.95 (0.71 ~ 1.25) 1.30 (0.93 ~ 1.82) 2.47 (1.23 ~ 4.95)	0.118 0.694 0.120 0.011
Heart failure Event = 302 N = 10662	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	46 / 2594 98 / 3082 105 / 3299 46 / 1518 7 / 169		1 (Ref) 1.11 (0.78 ~ 1.59) 1.02 (0.71 ~ 1.46) 1.41 (0.93 ~ 2.15) 3.48 (1.56 ~ 7.76)	0.557 0.918 0.106 0.002
Diabetic retinopathy Event = 261 N = 8509	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	20 / 2176 64 / 2533 117 / 2525 51 / 1143 9 / 132		1 (Ref) 1.40 (0.84 ~ 2.32) 2.57 (1.59 ~ 4.16) 3.60 (2.13 ~ 6.10) 9.57 (4.30 ~ 21.32)	0.197 <0.001 <0.001 <0.001
Diabetic peripheral neuropathy Event = 1212 N = 7636	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	184 / 1916 360 / 2278 445 / 2293 193 / 1018 30 / 131	⊨= == ==	1 (Ref) 1.06 (0.89 ~ 1.27) 1.26 (1.06 ~ 1.51) 1.58 (1.29 ~ 1.95) 3.66 (2.48 ~ 5.40)	0.507 0.010 <0.001 <0.001
Diabetic foot ulcer Event = 229 N = 8856	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	20 / 2185 59 / 2649 97 / 2690 46 / 1195 7 / 137		1 (Ref) 1.42 (0.85 ~ 2.37) 2.12 (1.30 ~ 3.46) 3.05 (1.78 ~ 5.20) 6.27 (2.62 ~ 15.00)	0.177 0.003 <0.001 <0.001
Chronic kidney disease Event = 925 N = 9643	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	157 / 2343 304 / 2742 309 / 2953 132 / 1433 23 / 172		1 (Ref) 1.01 (0.83 ~ 1.23) 0.92 (0.76 ~ 1.12) 1.19 (0.94 ~ 1.51) 2.73 (1.76 ~ 4.23)	0.941 0.417 0.151 <0.001

0.50 2.0 8.0

B.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE					
Event = 1481	>=0 to <=20	519 / 3300	- +	1 (Ref)	
N = 7472	>20 to <=40	462 / 2189	1	0.95 (0.84 ~ 1.08)	0.427
	>40 to <=60	355/1426	E.	$1.21(1.06 \sim 1.39)$ $1.63(1.35 \sim 1.97)$	<0.006
	>80 to <=100	7/41	H	1.59 (0.75 ~ 3.36)	0.222
All-cause mortality					
Event = 2858	>=0 to <=20	993 / 3890	+	1 (Ref)	
N = 8964	>20 to <=40	873 / 2631		0.93 (0.85 ~ 1.02)	0.129
	>40 to <=60	706 / 1758	H	1.17 (1.06 ~ 1.29)	0.002
	>60 to <=80 >80 to <=100	270 / 642 16 / 43	H	$1.55 (1.35 \sim 1.78)$ $2.07 (1.26 \sim 3.40)$	<0.001 0.004
Atherosclerotic cardiovascular death				. ,	
Event = 594	>=0 to <=20	187 / 3831	+	1 (Ref)	
N = 8849	>20 to <=40	197 / 2607	H=1	1.05 (0.86 ~ 1.28)	0.645
	>40 to <=60	161 / 1740	H	1.32 (1.07 ~ 1.64)	0.011
	>60 to <=80 >80 to <=100	48 / 627 1 / 44		$1.40(1.02 \sim 1.92)$ 0.71(0.10 ~ 5.07)	0.040
Coronany arteny disease				,	
Event = 1259	>=0 to <=20	426 / 3045	+	1 (Ref)	
N = 6952	>20 to <=40	415 / 2052	+	1.05 (0.92 ~ 1.21)	0.473
	>40 to <=60	294 / 1328	H	1.21 (1.04 ~ 1.41)	0.014
	>60 to <=80	118 / 487	H	1.62 (1.32 ~ 1.99)	<0.001
	>80 to <=100	6/40		1.77 (0.79 ~ 3.97)	0.165
Ischemic stroke					
Event = 719	>=0 to <=20	286/3579	Ĵ	1 (Ref)	0.000
N = 8169	>20 to <=40 >40 to <=60	208/2380	1	$0.81(0.68 \sim 0.97)$ 1.00(0.82 ~ 1.21)	0.022
	>60 to <=80	66 / 579		$1.38(1.05 \sim 1.80)$	0.020
	>80 to <=100	2 / 42	⊢ •−−+	0.81 (0.20 ~ 3.27)	0.769
Heart failure					
Event = 551	>=0 to <=20	197 / 3692	+	1 (Ref)	
N = 8397	>20 to <=40	159 / 2456	H.	0.90 (0.73 ~ 1.12)	0.342
	>40 to <=60	134 / 1633	H=1	1.20 (0.96 ~ 1.51)	0.104
	>80 to <=80	4/41	-=-	$1.82(1.36 \sim 2.46)$ $2.66(0.99 \sim 7.19)$	<0.001 0.054
Diabetic retinopathy					
Event = 153	>=0 to <=20	41 / 2903	+	1 (Ref)	
N = 6558	>20 to <=40	44 / 1929	H 4 -1	0.99 (0.65 ~ 1.53)	0.976
	>40 to <=60	47 / 1227		1.53 (1.00 ~ 2.34)	0.053
	>60 to <=80	19/462		$2.44 (1.40 \sim 4.22)$ 6 23 (1 50 ~ 25 93)	0.002
	20010 -100	2151		0.25 (1.50 * 25.55)	0.012
Diabetic peripheral neuropathy	>=0 to <=20	466 / 2435	_	1 (Pof)	
N = 5475	>20 to <=20	439 / 1607	L L	$1 17 (1 02 \sim 1.33)$	0.021
	>40 to <=60	302 / 1019	H	1.30 (1.12 ~ 1.50)	0.001
	>60 to <=80	96 / 376	H - 1	1.28 (1.03 ~ 1.60)	0.028
	>80 to <=100	11 / 38	H•-1	2.04 (1.12 ~ 3.71)	0.020
Diabetic foot ulcer					
Event = 239	>=0 to <=20	67 / 3068		1 (Ref)	
N = 7057	>20 to <=40	69 / 2082	H=-1	1.12 (0.80 ~ 1.58)	0.502
	>40 to <=60	/4 / 1365	H-1	$1.96(1.40 \sim 2.74)$	< 0.001
	>80 to <=100	2/499		3.34 (0.81 ~ 13.69)	0.094
Chronic kidnev disease					
Event = 797	>=0 to <=20	254 / 1817	+	1 (Ref)	
N = 4169	>20 to <=40	250 / 1162	Hel	1.07 (0.90 ~ 1.28)	0.459
	>40 to <=60	209 / 856	-	1.21 (1.00 ~ 1.45)	0.050
	>60 to <=80	12/301		$1.49(1.14 \sim 1.94)$	0.003
	-0010 -100	12/33		3.41 (1.81 ~ 0.10)	~0.001
		Γ			
		0.1	10 1.0 4.0		

A. the subgroup of patients younger than 65; B. the subgroup of patients aged 65 or older

Figure S3. The subgroup analysis based on sex

A.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1102 N = 8164	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	329 / 2938 339 / 2408 307 / 1968 121 / 786 6 / 64	H HH HH	1 (Ref) 1.05 (0.90 ~ 1.23) 1.47 (1.25 ~ 1.73) 2.06 (1.67 ~ 2.56) 2.07 (0.92 ~ 4.66)	0.553 <0.001 <0.001 0.079
All-cause mortality Event = 1918 N = 9029	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	595 / 3242 578 / 2653 522 / 2181 209 / 880 14 / 73	₩ ₩ -+	1 (Ref) 0.99 (0.88 ~ 1.11) 1.37 (1.21 ~ 1.55) 1.93 (1.64 ~ 2.26) 2.90 (1.70 ~ 4.94)	0.866 <0.001 <0.001 <0.001
Atherosclerotic cardiovascular death Event = 391 N = 8969	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	102 / 3217 137 / 2638 116 / 2169 34 / 873 2 / 72		1 (Ref) 1.33 (1.03 ~ 1.74) 1.69 (1.28 ~ 2.24) 1.75 (1.18 ~ 2.60) 2.70 (0.66 ~ 11.02)	0.031 <0.001 0.005 0.166
Coronary artery disease Event = 968 N = 7819	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	287 / 2826 292 / 2282 284 / 1885 97 / 759 8 / 67	= = == -=-	1 (Ref) 0.98 (0.83 ~ 1.16) 1.35 (1.14 ~ 1.61) 1.55 (1.22 ~ 1.96) 2.43 (1.20 ~ 4.94)	0.812 0.001 <0.001 0.014
Ischemic stroke Event = 552 N = 8529	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	191 / 3060 155 / 2510 145 / 2060 59 / 831 2 / 68		1 (Ref) 0.84 (0.68 ~ 1.05) 1.19 (0.95 ~ 1.50) 1.65 (1.22 ~ 2.22) 1.04 (0.26 ~ 4.22)	0.118 0.128 0.001 0.953
Heart failure Event = 397 N = 8730	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	123 / 3155 128 / 2561 92 / 2093 51 / 847 3 / 74	⊨+ ⊨=+ ⊨=+	1 (Ref) 1.13 (0.88 ~ 1.46) 1.19 (0.90 ~ 1.59) 2.30 (1.65 ~ 3.22) 2.61 (0.82 ~ 8.27)	0.333 0.220 <0.001 0.104
Diabetic retinopathy Event = 182 N = 6861	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	30 / 2536 50 / 2024 66 / 1604 29 / 629 7 / 68		1 (Ref) 1.17 (0.74 ~ 1.86) 1.93 (1.23 ~ 3.02) 3.40 (2.01 ~ 5.77) 15.74 (6.74 ~ 36.73)	0.496 0.004 <0.001 <0.001
Diabetic peripheral neuropathy Event = 1135 N = 6050	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	324 / 2179 353 / 1784 326 / 1450 113 / 571 19 / 66	iei ei ≠i -=-1	1 (Ref) 1.12 (0.96 ~ 1.31) 1.39 (1.19 ~ 1.64) 1.60 (1.28 ~ 1.99) 4.92 (3.08 ~ 7.85)	0.154 <0.001 <0.001 <0.001
Diabetic foot ulcer Event = 187 N = 7336	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	36 / 2651 55 / 2175 69 / 1749 26 / 694 1 / 67		1 (Ref) 1.45 (0.94 ~ 2.22) 2.64 (1.73 ~ 4.03) 3.61 (2.14 ~ 6.07) 2.69 (0.36 ~ 19.82)	0.092 <0.001 <0.001 0.332
Chronic kidney disease Event = 722 N = 5394	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	187 / 1744 238 / 1566 198 / 1388 86 / 625 13 / 71	4 + -■-	1 (Ref) 1.01 (0.83 ~ 1.23) 1.04 (0.84 ~ 1.28) 1.32 (1.02 ~ 1.72) 2.81 (1.60 ~ 4.96)	0.931 0.728 0.037 <0.001
		0.	20 1.0 4.016.0		

B.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE					
Event = 1287	>=0 to <=20	333 / 2755	+	1 (Ref)	
N = 9202	>20 to <=40	375 / 2642	H.	0.95 (0.82 ~ 1.11)	0.537
	>40 to <=60	380 / 2542		$1.15(0.98 \sim 1.34)$ $1.75(1.45 \sim 2.11)$	0.080
	>80 to <=100	20 / 128		$2.41(1.53 \sim 3.80)$	<0.001
All-cause mortality					
Event = 2172	>=0 to <=20	610 / 3291	•	1 (Ref)	
N = 10854	>20 to <=40	630 / 3126	H	0.93 (0.83 ~ 1.04)	0.218
	>40 to <=60	621/2979	H-1	1.14 (1.02 ~ 1.28)	0.023
	>60 to <=80 >80 to <=100	288 / 1321 23 / 137	H=	$1.80(1.55 \sim 2.07)$ 2.10(1.38 ~ 3.19)	<0.001 0.001
Atherosclerotic cardiovascular death				. ,	
Event = 501	>=0 to <=20	124 / 3251	+	1 (Ref)	
N = 10777	>20 to <=40	152 / 3114	H•-1	0.98 (0.77 ~ 1.25)	0.887
	>40 to <=60	153 / 2964	H=-1	1.18 (0.92 ~ 1.51)	0.189
	>60 to <=80 >80 to <=100	5/1310		$1.79(1.32 \sim 2.43)$ $2.24(0.91 \sim 5.50)$	<0.001 0.079
Coronary artery disease				,	
Event = 1260	>=0 to <=20	316 / 2559	ł	1 (Ref)	
N = 8594	>20 to <=40	406 / 2499	H = -I	1.08 (0.93 ~ 1.25)	0.337
	>40 to <=60	338 / 2343		1.07 (0.91 ~ 1.25)	0.427
	>80 to <=80	21/122		$2.77 (1.77 \sim 4.33)$	<0.001
lechamic stroka					
Event = 584	>=0 to <=20	174 / 3025	•	1 (Ref)	
N = 10080	>20 to <=40	166 / 2888	H=-1	0.84 (0.68 ~ 1.04)	0.116
	>40 to <=60	161 / 2791	H - H	0.96 (0.77 ~ 1.20)	0.720
	>60 to <=80 >80 to <=100	74 / 1239 9 / 137		$1.41(1.07 \sim 1.87)$ $2.57(1.31 \sim 5.04)$	0.016
Event = 456	>=0 to <=20	120/3131		1 (Ref)	
N = 10329	>20 to <=40	129 / 2977	Held I	0.95 (0.74 ~ 1.22)	0.693
	>40 to <=60	147 / 2839	⊢ •-1	1.32 (1.02 ~ 1.69)	0.032
	>60 to <=80	52 / 1246	H=	1.57 (1.12 ~ 2.19)	0.009
	>80 to <=100	8/130		3.54 (1.72 ~ 7.28)	0.001
Diabetic retinopathy	>=0 to <=20	21/05/2		1 (Pof)	
N = 8206	>20 to <=40	58/2438	i i i i i i i i i i i i i i i i i i i	$1.08(0.70 \sim 1.69)$	0 723
11 0200	>40 to <=60	98/2148		1.98 (1.30 ~ 3.01)	0.001
	>60 to <=80	41 / 976		2.58 (1.59 ~ 4.18)	<0.001
	>80 to <=100	4 / 101		3.54 (1.22 ~ 10.25)	0.020
Diabetic peripheral neuropathy					
Event = 1391	>=0 to <=20	326/21/2	L	1 (Ref)	0.046
11 = 7001	>40 to <=60	421 / 1862	H-H	$1.33(1.14 \sim 1.54)$	<0.040
	>60 to <=80	176 / 823	H=H	1.59 (1.32 ~ 1.92)	< 0.001
	>80 to <=100	22 / 103		2.33 (1.51 ~ 3.60)	<0.001
Diabetic foot ulcer					
Event = 281	>=0 to <=20	51 / 2602		1 (Ref)	0.070
N = 8577	>20 to <=40	102/2006		$1.08(0.75 \sim 1.55)$ $1.72(1.21 \sim 2.44)$	0.679
	>60 to <=80	47 / 1000		$2.63(1.75 \sim 3.96)$	<0.002
	>80 to <=100	8 / 113		5.24 (2.45 ~ 11.22)	<0.001
Chronic kidney disease					
Event = 1000	>=0 to <=20	224 / 2416	t.	1 (Ref)	0.000
N = 8418	>20 to <=40	316 / 2338		$1.20(1.01 \sim 1.43)$ $1.33(1.12 \sim 1.50)$	0.039
	>60 to <=80	118 / 1109		$1.33(1.12 \approx 1.39)$ $1.72(1.37 \approx 2.17)$	<0.001
	>80 to <=100	22 / 134		4.13 (2.64 ~ 6.45)	<0.001
		0.	50 2.04.08.0		

A. the subgroup of female patients; B. the subgroup of male patients Abbreviations: CI: confidence interval; HR: hazard ratio.

Figure S4. The subgroup analysis based on the baseline body mass

A.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1216 N = 10330	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	303 / 3040 345 / 2936 372 / 2915 176 / 1313 20 / 126	↓ + ++ -+-	1 (Ref) 0.99 (0.85 ~ 1.16) 1.19 (1.02 ~ 1.40) 1.80 (1.48 ~ 2.18) 2.77 (1.75 ~ 4.38)	0.927 0.029 <0.001 <0.001
All-cause mortality Event = 1910 N = 11679	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	481 / 3439 576 / 3345 575 / 3282 261 / 1477 17 / 136	₩ ₩ ₩ ₩	1 (Ref) 1.05 (0.93 ~ 1.18) 1.25 (1.10 ~ 1.42) 1.92 (1.64 ~ 2.24) 1.84 (1.13 ~ 2.99)	0.460 0.001 <0.001 0.014
Atherosclerotic cardiovascular death Event = 447 N = 11615	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	90 / 3408 139 / 3332 152 / 3272 59 / 1468 7 / 135		1 (Ref) 1.25 (0.95 ~ 1.63) 1.54 (1.17 ~ 2.02) 2.08 (1.48 ~ 2.92) 3.79 (1.74 ~ 8.25)	0.109 0.002 <0.001 0.001
Coronary artery disease Event = 1169 N = 9676	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	280 / 2859 350 / 2768 359 / 2694 161 / 1232 19 / 123	⊨= == -=-	1 (Ref) 1.08 (0.92 ~ 1.26) 1.20 (1.02 ~ 1.41) 1.61 (1.32 ~ 1.97) 2.28 (1.43 ~ 3.66)	0.372 0.030 <0.001 0.001
Ischemic stroke Event = 576 N = 11028	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	185 / 3229 150 / 3135 156 / 3118 76 / 1410 9 / 136		1 (Ref) 0.72 (0.58 ~ 0.90) 0.84 (0.67 ~ 1.06) 1.27 (0.96 ~ 1.68) 2.30 (1.17 ~ 4.51)	0.004 0.141 0.088 0.016
Heart failure Event = 487 N = 11234	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	138 / 3323 144 / 3213 141 / 3146 59 / 1417 5 / 135		1 (Ref) 0.96 (0.76 ~ 1.21) 1.11 (0.87 ~ 1.43) 1.54 (1.12 ~ 2.11) 1.99 (0.81 ~ 4.89)	0.722 0.397 0.007 0.132
Diabetic retinopathy Event = 225 N = 8908	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	28 / 2706 55 / 2620 93 / 2386 43 / 1083 6 / 113		1 (Ref) 1.22 (0.77 ~ 1.93) 2.13 (1.38 ~ 3.30) 3.21 (1.96 ~ 5.26) 6.23 (2.52 ~ 15.38)	0.403 0.001 <0.001 <0.001
Diabetic peripheral neuropathy Event = 1317 N = 7621	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	302 / 2279 405 / 2234 413 / 2079 172 / 921 25 / 108	⊨=+ =+ -=-	1 (Ref) 1.10 (0.95 ~ 1.29) 1.26 (1.07 ~ 1.47) 1.54 (1.26 ~ 1.87) 3.33 (2.20 ~ 5.03)	0.205 0.004 <0.001 <0.001
Diabetic foot ulcer Event = 226 N = 9249	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	40 / 2781 65 / 2725 74 / 2520 40 / 1107 7 / 116		1 (Ref) 1.20 (0.80 ~ 1.79) 1.42 (0.95 ~ 2.12) 2.43 (1.54 ~ 3.84) 5.54 (2.43 ~ 12.60)	0.379 0.090 <0.001 <0.001
Chronic kidney disease Event = 936 N = 8553	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	214 / 2318 295 / 2381 287 / 2494 124 / 1233 16 / 127		1 (Ref) 1.12 (0.93 ~ 1.34) 1.14 (0.95 ~ 1.38) 1.45 (1.15 ~ 1.83) 2.60 (1.55 ~ 4.36)	0.221 0.156 0.002 <0.001
		0.	50 2.04.08.0		

B.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1173 N = 7036	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	359 / 2653 369 / 2114 315 / 1595 124 / 608 6 / 66	iei jai jai	1 (Ref) 1.00 (0.86 ~ 1.16) 1.36 (1.16 ~ 1.60) 1.97 (1.60 ~ 2.43) 1.53 (0.68 ~ 3.44)	0.977 <0.001 <0.001 0.303
All-cause mortality Event = 2180 N = 8204	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	724 / 3094 632 / 2434 568 / 1878 236 / 724 20 / 74	H H	1 (Ref) 0.89 (0.80 ~ 1.00) 1.23 (1.10 ~ 1.38) 1.79 (1.54 ~ 2.08) 3.26 (2.08 ~ 5.09)	0.047 <0.001 <0.001 <0.001
Atherosclerotic cardiovascular death Event = 445 N = 8131	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	136 / 3060 150 / 2420 117 / 1861 42 / 715 0 / 75	- 	1 (Ref) 1.06 (0.84 ~ 1.35) 1.24 (0.96 ~ 1.61) 1.60 (1.13 ~ 2.27)	0.620 0.096 0.008 0.990
Coronary artery disease Event = 1059 N = 6737	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	323 / 2526 348 / 2013 263 / 1534 115 / 598 10 / 66	+ 	1 (Ref) 1.00 (0.85 ~ 1.17) 1.13 (0.96 ~ 1.34) 1.75 (1.41 ~ 2.17) 3.51 (1.86 ~ 6.61)	0.975 0.149 <0.001 <0.001
Ischemic stroke Event = 560 N = 7581	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	180 / 2856 171 / 2263 150 / 1733 57 / 660 2 / 69	= = += 	1 (Ref) 0.96 (0.78 ~ 1.20) 1.33 (1.06 ~ 1.67) 1.79 (1.32 ~ 2.42) 1.19 (0.30 ~ 4.82)	0.734 0.013 <0.001 0.805
Heart failure Event = 366 N = 7825	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	105 / 2963 113 / 2325 98 / 1786 44 / 676 6 / 75	• +•-! ⊢•=-!	1 (Ref) 1.13 (0.86 ~ 1.48) 1.49 (1.12 ~ 1.98) 2.46 (1.72 ~ 3.51) 5.94 (2.59 ~ 13.62)	0.396 0.006 <0.001 <0.001
Diabetic retinopathy Event = 189 N = 6159	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	33 / 2373 53 / 1842 71 / 1366 27 / 522 5 / 56		1 (Ref) 1.04 (0.66 ~ 1.62) 1.79 (1.17 ~ 2.76) 2.56 (1.52 ~ 4.32) 11.92 (4.59 ~ 30.96)	0.872 0.008 <0.001 <0.001
Diabetic peripheral neuropathy Event = 1209 N = 5490	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	348 / 2072 394 / 1651 334 / 1233 117 / 473 16 / 61	=i ≠ ≠=	1 (Ref) 1.16 (1.00 ~ 1.34) 1.45 (1.24 ~ 1.70) 1.62 (1.31 ~ 2.01) 2.74 (1.65 ~ 4.53)	0.050 <0.001 <0.001 <0.001
Diabetic foot ulcer Event = 242 N = 6664	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	47 / 2472 63 / 2006 97 / 1535 33 / 587 2 / 64		1 (Ref) 1.25 (0.85 ~ 1.83) 2.78 (1.94 ~ 3.99) 3.50 (2.22 ~ 5.52) 3.36 (0.81 ~ 13.91)	0.262 <0.001 <0.001 0.095
Chronic kidney disease Event = 786 N = 5259	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	197 / 1842 259 / 1523 231 / 1315 80 / 501 19 / 78		1 (Ref) 1.14 (0.94 ~ 1.38) 1.29 (1.06 ~ 1.57) 1.81 (1.39 ~ 2.36) 4.66 (2.89 ~ 7.50)	0.177 0.011 <0.001 <0.001
			0.50 2.0 8.0		

A. the subgroup of non-obese patients at baseline; B. the subgroup of obese patients at baseline

Figure S5. The subgroup analysis based on the time-weighted average HbA1c

A.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1016 N = 7999	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	559 / 4884 317 / 2251 116 / 727 20 / 128 4 / 9		1 (Ref) 1.03 (0.90 ~ 1.19) 1.62 (1.32 ~ 1.99) 2.35 (1.50 ~ 3.67) 7.05 (2.60 ~ 19.07)	0.651 <0.001 <0.001 <0.001
All-cause mortality Event = 1985 N = 9292	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	1058 / 5634 639 / 2656 240 / 852 45 / 140 3 / 10	H H	1 (Ref) 1.11 (1.01 ~ 1.23) 1.77 (1.54 ~ 2.05) 2.90 (2.15 ~ 3.92) 3.03 (0.97 ~ 9.47)	0.036 <0.001 <0.001 0.056
Atherosclerotic cardiovascular death Event = 395 N = 9216	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	202 / 5582 143 / 2643 48 / 843 2 / 138 0 / 10		1 (Ref) 1.24 (0.99 ~ 1.54) 1.76 (1.28 ~ 2.43) 0.66 (0.16 ~ 2.65)	0.057 0.001 0.556 0.989
Coronary artery disease Event = 910 N = 7531	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	491 / 4586 301 / 2132 104 / 683 12 / 122 2 / 8	• ++ 	1 (Ref) 1.10 (0.95 ~ 1.27) 1.60 (1.29 ~ 1.99) 1.60 (0.90 ~ 2.85) 3.72 (0.92 ~ 15.07)	0.203 <0.001 0.108 0.066
Ischemic stroke Event = 516 N = 8593	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	306 / 5231 138 / 2426 57 / 793 13 / 133 2 / 10		1 (Ref) 0.83 (0.68 ~ 1.02) 1.43 (1.07 ~ 1.90) 2.83 (1.62 ~ 4.94) 7.38 (1.82 ~ 29.99)	0.079 0.016 <0.001 0.005
Heart failure Event = 371 N = 8878	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	214 / 5412 104 / 2517 46 / 809 6 / 129 1 / 11		1 (Ref) 0.95 (0.75 ~ 1.20) 1.81 (1.31 ~ 2.51) 2.08 (0.92 ~ 4.69) 6.57 (0.91 ~ 47.37)	0.654 <0.001 0.078 0.062
Diabetic retinopathy Event = 80 N = 6809	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	38 / 4191 25 / 1901 14 / 602 3 / 109 0 / 6		1 (Ref) 0.99 (0.59 ~ 1.66) 2.03 (1.08 ~ 3.82) 4.47 (1.33 ~ 14.99)	0.974 0.027 0.015 0.996
Diabetic peripheral neuropathy Event = 922 N = 5759	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	473 / 3519 310 / 1619 120 / 524 18 / 87 1 / 10		1 (Ref) 1.27 (1.09 ~ 1.47) 1.90 (1.55 ~ 2.32) 1.90 (1.19 ~ 3.05) 1.77 (0.25 ~ 12.71)	0.001 <0.001 0.008 0.569
Diabetic foot ulcer Event = 151 N = 7109	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	77 / 4348 50 / 2030 19 / 619 5 / 103 0 / 9		1 (Ref) 1.21 (0.84 ~ 1.73) 1.86 (1.12 ~ 3.09) 3.90 (1.56 ~ 9.72)	0.311 0.017 0.003 0.994
Chronic kidney disease Event = 637 N = 5875	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	300 / 3474 217 / 1677 98 / 610 20 / 104 2 / 10		1 (Ref) 1.22 (1.02 ~ 1.46) 1.81 (1.43 ~ 2.28) 3.51 (2.23 ~ 5.54) 3.16 (0.75 ~ 13.20)	0.028 <0.001 <0.001 0.116

0.20 1.0 4.0 32.0

В.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1373 N = 9367	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	103 / 809 397 / 2799 571 / 3783 280 / 1793 22 / 183		1 (Ref) 0.85 (0.68 ~ 1.06) 1.05 (0.85 ~ 1.30) 1.58 (1.26 ~ 1.99) 1.80 (1.14 ~ 2.87)	0.152 0.659 <0.001 0.013
All-cause mortality Event = 2105 N = 10591	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	147 / 899 569 / 3123 903 / 4308 452 / 2061 34 / 200		1 (Ref) 0.82 (0.68 ~ 0.98) 1.13 (0.95 ~ 1.35) 1.77 (1.47 ~ 2.14) 2.34 (1.61 ~ 3.41)	0.034 0.174 <0.001 <0.001
Atherosclerotic cardiovascular death Event = 497 N = 10530	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	24 / 886 146 / 3109 221 / 4290 99 / 2045 7 / 200		1 (Ref) 1.17 (0.76 ~ 1.80) 1.46 (0.95 ~ 2.24) 2.12 (1.35 ~ 3.32) 2.95 (1.26 ~ 6.87)	0.484 0.082 0.001 0.012
Coronary artery disease Event = 1318 N = 8882	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	112 / 799 397 / 2649 518 / 3545 264 / 1708 27 / 181	-=- -=- -=-	1 (Ref) 0.78 (0.63 ~ 0.96) 0.83 (0.67 ~ 1.02) 1.23 (0.98 ~ 1.54) 1.91 (1.25 ~ 2.92)	0.020 0.076 0.068 0.003
Ischemic stroke Event = 620 N = 10016	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	59 / 854 183 / 2972 249 / 4058 120 / 1937 9 / 195		1 (Ref) 0.70 (0.52 ~ 0.95) 0.83 (0.62 ~ 1.10) 1.19 (0.86 ~ 1.63) 1.45 (0.71 ~ 2.93)	0.020 0.195 0.291 0.305
Heart failure Event = 482 N = 10181	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	29 / 874 153 / 3021 193 / 4123 97 / 1964 10 / 199		1 (Ref) 1.19 (0.80 ~ 1.78) 1.28 (0.86 ~ 1.91) 2.05 (1.35 ~ 3.12) 3.58 (1.73 ~ 7.38)	0.394 0.217 0.001 0.001
Diabetic retinopathy Event = 334 N = 8258	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	23 / 888 83 / 2561 150 / 3150 67 / 1496 11 / 163		1 (Ref) 0.71 (0.45 ~ 1.13) 1.03 (0.66 ~ 1.61) 1.44 (0.89 ~ 2.33) 3.53 (1.70 ~ 7.32)	0.152 0.903 0.139 0.001
Diabetic peripheral neuropathy Event = 1604 N = 7352	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	177 / 832 489 / 2266 627 / 2788 271 / 1307 40 / 159	H=1 H=1 H=1 H=1	1 (Ref) 0.75 (0.63 ~ 0.90) 0.82 (0.69 ~ 0.97) 1.00 (0.83 ~ 1.22) 2.02 (1.43 ~ 2.85)	0.001 0.023 0.964 <0.001
Diabetic foot ulcer Event = 317 N = 8804	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	10 / 905 78 / 2701 152 / 3436 68 / 1591 9 / 171		1 (Ref) 1.78 (0.92 ~ 3.45) 2.88 (1.51 ~ 5.51) 4.11 (2.10 ~ 8.04) 7.82 (3.15 ~ 19.40)	0.087 0.001 <0.001 <0.001
Chronic kidney disease Event = 1085 N = 7937	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	111 / 686 337 / 2227 420 / 3199 184 / 1630 33 / 195		1 (Ref) 0.78 (0.63 ~ 0.97) 0.78 (0.63 ~ 0.96) 1.05 (0.83 ~ 1.33) 2.51 (1.70 ~ 3.72)	0.023 0.021 0.697 <0.001
		0	.50 2.0 8.0		

A. the subgroup of the time-weighted average HbA1c \leq 7% (53 mmol/mol); B. the subgroup of the time-weighted average HbA1c >7% (53 mmol/mol) Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.

Figure S6. The subgroup analysis based on the treatment of diabetes at baseline

A.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1198 N = 9259	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	493 / 4212 354 / 2590 258 / 1799 84 / 607 9 / 51	= -=- =	1 (Ref) 0.95 (0.83 ~ 1.10) 1.18 (1.00 ~ 1.38) 1.59 (1.26 ~ 2.01) 2.55 (1.31 ~ 4.96)	0.506 0.045 <0.001 0.006
All-cause mortality Event = 2165 N = 10685	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	915 / 4849 627 / 3014 454 / 2079 155 / 689 14 / 54	₩ # -=	1 (Ref) 0.94 (0.84 ~ 1.04) 1.18 (1.05 ~ 1.33) 1.75 (1.47 ~ 2.09) 2.50 (1.47 ~ 4.24)	0.213 0.006 <0.001 0.001
Atherosclerotic cardiovascular death Event = 450 N = 10618	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	170 / 4805 136 / 3002 112 / 2071 30 / 686 2 / 54		1 (Ref) 1.03 (0.81 ~ 1.29) 1.44 (1.12 ~ 1.85) 1.76 (1.18 ~ 2.61) 2.02 (0.50 ~ 8.20)	0.824 0.005 0.005 0.324
Coronary artery disease Event = 1124 N = 8662	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	460 / 3961 336 / 2414 235 / 1667 84 / 569 9 / 51	₩ ₩ +# #	1 (Ref) 0.93 (0.80 ~ 1.07) 1.05 (0.89 ~ 1.24) 1.51 (1.19 ~ 1.91) 2.88 (1.47 ~ 5.62)	0.310 0.535 0.001 0.002
Ischemic stroke Event = 604 N = 9951	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	267 / 4512 170 / 2798 125 / 1949 39 / 639 3 / 53		1 (Ref) 0.87 (0.71 ~ 1.06) 1.08 (0.86 ~ 1.35) 1.40 (0.99 ~ 1.97) 1.76 (0.56 ~ 5.50)	0.163 0.518 0.057 0.333
Heart failure Event = 470 N = 10255	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	192 / 4667 135 / 2871 101 / 2007 38 / 655 4 / 55		1 (Ref) 1.01 (0.81 ~ 1.27) 1.25 (0.97 ~ 1.61) 2.08 (1.46 ~ 2.97) 3.88 (1.43 ~ 10.53)	0.935 0.081 <0.001 0.008
Diabetic retinopathy Event = 137 N = 8175	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	38 / 3766 36 / 2291 43 / 1568 17 / 503 3 / 47		1 (Ref) 0.81 (0.51 ~ 1.30) 1.42 (0.90 ~ 2.25) 2.61 (1.44 ~ 4.73) 6.96 (2.05 ~ 23.61)	0.383 0.132 0.002 0.002
Diabetic peripheral neuropathy Event = 1220 N = 7116	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	471 / 3269 389 / 2015 261 / 1332 84 / 453 15 / 47	⊨= == =_	1 (Ref) 1.06 (0.93 ~ 1.22) 1.20 (1.03 ~ 1.41) 1.36 (1.08 ~ 1.73) 3.05 (1.82 ~ 5.12)	0.376 0.023 0.010 <0.001
Diabetic foot ulcer Event = 185 N = 8601	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	64 / 3929 41 / 2441 64 / 1642 14 / 541 2 / 48		1 (Ref) 0.77 (0.51 ~ 1.14) 1.90 (1.31 ~ 2.74) 1.82 (1.00 ~ 3.29) 3.49 (0.84 ~ 14.58)	0.191 0.001 0.048 0.086
Chronic kidney disease Event = 809 N = 7034	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	272 / 2963 263 / 1973 189 / 1517 78 / 533 7 / 48		$\begin{array}{c} 1 \ ({\sf Ref}) \\ 1.02 \ (0.86 \sim 1.22) \\ 1.02 \ (0.84 \sim 1.23) \\ 2.01 \ (1.55 \sim 2.60) \\ 2.62 \ (1.22 \sim 5.63) \end{array}$	0.820 0.873 <0.001 0.013

0.50 2.0 8.0

В.

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1191 N = 8107	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	169 / 1481 360 / 2460 429 / 2711 216 / 1314 17 / 141		1 (Ref) 0.96 (0.80 ~ 1.15) 1.23 (1.03 ~ 1.48) 1.86 (1.52 ~ 2.28) 2.05 (1.24 ~ 3.39)	0.661 0.024 <0.001 0.005
All-cause mortality Event = 1925 N = 9198	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	290 / 1684 581 / 2765 689 / 3081 342 / 1512 23 / 156		1 (Ref) 0.90 (0.78 ~ 1.04) 1.17 (1.02 ~ 1.34) 1.72 (1.47 ~ 2.02) 2.14 (1.40 ~ 3.27)	0.160 0.029 <0.001 <0.001
Atherosclerotic cardiovascular death Event = 442 N = 9128	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	56 / 1663 153 / 2750 157 / 3062 71 / 1497 5 / 156		1 (Ref) 1.14 (0.83 ~ 1.55) 1.22 (0.89 ~ 1.66) 1.68 (1.18 ~ 2.39) 2.34 (0.93 ~ 5.85)	0.418 0.215 0.004 0.070
Coronary artery disease Event = 1104 N = 7751	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	143 / 1424 362 / 2367 387 / 2561 192 / 1261 20 / 138		1 (Ref) 1.18 (0.97 ~ 1.43) 1.30 (1.07 ~ 1.58) 1.83 (1.47 ~ 2.28) 2.66 (1.66 ~ 4.26)	0.104 0.009 <0.001 <0.001
Ischemic stroke Event = 532 N = 8658	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	98 / 1573 151 / 2600 181 / 2902 94 / 1431 8 / 152		1 (Ref) 0.70 (0.54 ~ 0.90) 0.90 (0.70 ~ 1.16) 1.33 (0.99 ~ 1.77) 1.80 (0.87 ~ 3.70)	0.006 0.403 0.055 0.113
Heart failure Event = 383 N = 8804	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	51 / 1619 122 / 2667 138 / 2925 65 / 1438 7 / 155		1 (Ref) 1.10 (0.79 ~ 1.53) 1.36 (0.98 ~ 1.89) 1.90 (1.31 ~ 2.76) 3.28 (1.48 ~ 7.25)	0.578 0.066 0.001 0.003
Diabetic retinopathy Event = 277 N = 6892	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	23 / 1313 72 / 2171 121 / 2184 53 / 1102 8 / 122		1 (Ref) 1.07 (0.67 ~ 1.72) 1.67 (1.06 ~ 2.63) 2.11 (1.28 ~ 3.47) 4.92 (2.18 ~ 11.11)	0.776 0.027 0.003 <0.001
Diabetic peripheral neuropathy Event = 1306 N = 5995	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	179 / 1082 410 / 1870 486 / 1980 205 / 941 26 / 122	• ++ ++ -+-	1 (Ref) 1.13 (0.95 ~ 1.36) 1.32 (1.11 ~ 1.57) 1.54 (1.25 ~ 1.88) 2.88 (1.90 ~ 4.36)	0.162 0.002 <0.001 <0.001
Diabetic foot ulcer Event = 283 N = 7312	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	23 / 1324 87 / 2290 107 / 2413 59 / 1153 7 / 132		1 (Ref) 1.62 (1.02 ~ 2.57) 2.01 (1.27 ~ 3.17) 3.26 (2.00 ~ 5.30) 5.51 (2.35 ~ 12.92)	0.041 0.003 <0.001 <0.001
Chronic kidney disease Event = 913 N = 6778	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	139 / 1197 291 / 1931 329 / 2292 126 / 1201 28 / 157		1 (Ref) 1.04 (0.85 ~ 1.27) 1.16 (0.95 ~ 1.43) 1.16 (0.91 ~ 1.49) 3.12 (2.07 ~ 4.69)	0.720 0.146 0.227 <0.001
		0.	50 2.04.08.0		

A. the subgroup of patients receiving lifestyle intervention only at baseline; B. the subgroup of patients receiving anti-diabetic medication or insulin at baseline Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.

Figure S7. The sensitivity analysis using the binned HbA1c variability score (b-HVS)

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE					
Event = 2273	>=0 to <=20	657 / 5649	. <u>.</u> .	1 (Ref)	0.004
N = 16605	>20 to <=40	600 / 4482		$0.99(0.89 \sim 1.11)$ 1 17 (1 04 \sim 1 32)	0.864
	>60 to <=80	330 / 2006		$1.17(1.04 \sim 1.32)$ $1.81(1.58 \sim 2.07)$	<0.007
	>80 to <=100	40 / 274	⊢ ∎–1	2.45 (1.77 ~ 3.37)	< 0.001
All-cause mortality					
Event = 3843	>=0 to <=20	1178 / 6443	•	1 (Ref)	
N = 18983	>20 to <=40	1038 / 5119	H=1	0.92 (0.85 ~ 1.01)	0.066
	>40 to <=60	1039 / 4803	H	1.18 (1.09 ~ 1.29)	< 0.001
	>60 to <=80 >80 to <=100	520 / 2299 68 / 319		$1.71(1.54 \sim 1.90)$ $2.62(2.05 \sim 3.35)$	<0.001 <0.001
Atherosclerotic cardiovascular death					
Event = 855	>=0 to <=20	237 / 6418		1 (Ref)	
N = 18917	>20 to <=40	252 / 5101	H - -1	1.02 (0.85 ~ 1.22)	0.851
	>40 to <=60	234 / 4790	+	1.16 (0.96 ~ 1.40)	0.123
	>60 to <=80	118 / 2291		1.70 (1.35 ~ 2.13)	< 0.001
	>80 to <=100	14/31/		2.47 (1.44 ~ 4.25)	0.001
Coronary artery disease Event = 2120	>=0 to <=20	605 / 5370	1	1 (Ref)	
N = 15672	>20 to <=40	604 / 4219	H-I	$1.00(0.89 \sim 1.12)$	0 998
	>40 to <=60	580 / 3937	H=H	1.14 (1.01 ~ 1.29)	0.029
	>60 to <=80	282 / 1873	H	1.54 (1.33 ~ 1.78)	< 0.001
	>80 to <=100	49 / 273	H	2.74 (2.04 ~ 3.68)	<0.001
Ischemic stroke					
Event = 1078	>=0 to <=20	343 / 6016	•	1 (Ref)	
N = 17810	>20 to <=40	305 / 4809	H=H	0.94 (0.80 ~ 1.10)	0.452
	>40 to <=60	268 / 4523	H•1	1.02 (0.87 ~ 1.21)	0.776
	>80 to <=100	17 / 293		2.00 (1.23 ~ 3.27)	0.005
Heart failure					
Event = 816	>=0 to <=20	246 / 6244		1 (Ref)	
N = 18253	>20 to <=40	220 / 4902	H=1	0.96 (0.80 ~ 1.15)	0.657
	>40 to <=60	216 / 4605	⊢ ∎-1	1.17 (0.97 ~ 1.42)	0.101
	>60 to <=80	117 / 2194	H=	1.81 (1.44 ~ 2.27)	<0.001
	>80 to <=100	17 / 308	I	2.78 (1.69 ~ 4.56)	<0.001
Diabetic retinopathy					
Event = 399	>=0 to <=20	66/5044		1 (Ref)	0 404
N = 14443	>20 to <=40	102/3961		$1.12(0.82 \sim 1.53)$ $1.69(1.24 \sim 2.29)$	0.491
	>60 to <=80	78 / 1639		$2.52(1.79 \sim 3.54)$	<0.001
	>80 to <=100	10 / 237	⊢ •−−1	3.94 (2.00 ~ 7.77)	<0.001
Diabetic peripheral neuropathy					
Event = 2404	>=0 to <=20	679 / 4352	•	1 (Ref)	
N = 12595	>20 to <=40	674 / 3495	H+I	0.97 (0.87 ~ 1.08)	0.588
	>40 to <=60	668 / 3069	H=1	1.18 (1.05 ~ 1.32)	0.004
	>80 to <=80	318 / 1452 65 / 227		$1.48(1.28 \sim 1.69)$ $3.13(2.42 \sim 4.05)$	< 0.001
Dishetis feet view				. ,	
Event = 456	>=0 to <=20	89/5237		1 (Ref)	
N = 15381	>20 to <=40	116 / 4276	H	1.17 (0.88 ~ 1.55)	0.275
	>40 to <=60	144 / 3846	H	1.73 (1.31 ~ 2.28)	< 0.001
	>60 to <=80	96 / 1778	H	3.33 (2.46 ~ 4.50)	<0.001
	>80 to <=100	11 / 244		4.62 (2.45 ~ 8.71)	<0.001
Chronic kidney disease					
Event = 1671	>=0 to <=20	444 / 4134	1.	1 (Ref)	0.550
N = 131/6	>20 to <=40	499/3465	T	$1.04(0.91 \sim 1.19)$ 1.10(0.97 - 1.09)	0.553
	>60 to <=80	201/1769	1	$1.10(0.97 \sim 1.26)$ $1.25(1.05 \sim 1.26)$	0.147
	>80 to <=100	33 / 268	_ ⊢ ⊷	1.94 (1.35 ~ 2.77)	<0.001
				(
			1.0 2.0 4.0 8.0)	

Figure S8. The sensitivity analysis using the HbA1c variability score (HVS) based on the HbA1c measurement in the first three years since diagnosis

Outcomes	HVS Categories	n / N		HR (95% CI)	P value
MACE Event = 1862 N = 13102	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	585 / 4930 516 / 3342 506 / 3075 225 / 1459 30 / 296		1 (Ref) 1.20 (1.06 ~ 1.35) 1.40 (1.23 ~ 1.58) 1.47 (1.25 ~ 1.72) 1.19 (0.82 ~ 1.71)	0.003 <0.001 <0.001 0.366
All-cause mortality Event = 3202 N = 14970	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	1037 / 5713 868 / 3781 847 / 3467 390 / 1665 60 / 344	iei iei iei	1 (Ref) 1.17 (1.06 ~ 1.28) 1.42 (1.29 ~ 1.56) 1.55 (1.37 ~ 1.74) 1.48 (1.14 ~ 1.93)	0.001 <0.001 <0.001 0.003
Atherosclerotic cardiovascular death Event = 699 N = 14833	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	194 / 5648 218 / 3754 197 / 3440 79 / 1647 11 / 344		1 (Ref) 1.48 (1.22 ~ 1.80) 1.64 (1.34 ~ 2.01) 1.52 (1.16 ~ 1.98) 1.42 (0.77 ~ 2.62)	<0.001 <0.001 0.002 0.256
Coronary artery disease Event = 1755 N = 12386	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	545 / 4646 483 / 3144 472 / 2915 221 / 1391 34 / 290		1 (Ref) 1.12 (0.99 ~ 1.27) 1.28 (1.13 ~ 1.46) 1.42 (1.21 ~ 1.67) 1.21 (0.85 ~ 1.71)	0.079 <0.001 <0.001 0.288
Ischemic stroke Event = 870 N = 14011	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	329 / 5291 207 / 3555 215 / 3274 104 / 1569 15 / 322		1 (Ref) 0.89 (0.75 ~ 1.06) 1.13 (0.94 ~ 1.35) 1.27 (1.01 ~ 1.59) 1.07 (0.64 ~ 1.81)	0.198 0.189 0.038 0.790
Heart failure Event = 679 N = 14342	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	230 / 5461 190 / 3648 162 / 3316 80 / 1584 17 / 333	► -=- -=-	1 (Ref) 1.11 (0.91 ~ 1.35) 1.15 (0.93 ~ 1.41) 1.32 (1.01 ~ 1.71) 1.67 (1.01 ~ 2.73)	0.302 0.191 0.039 0.044
Diabetic retinopathy Event = 354 N = 11404	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	67 / 4360 94 / 2923 115 / 2618 69 / 1252 9 / 251		1 (Ref) 1.34 (0.97 ~ 1.84) 1.79 (1.31 ~ 2.44) 2.57 (1.82 ~ 3.62) 2.55 (1.26 ~ 5.13)	0.072 <0.001 <0.001 0.009
Diabetic peripheral neuropathy Event = 2093 N = 9888	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	621 / 3665 604 / 2560 557 / 2323 260 / 1105 51 / 235		1 (Ref) 1.22 (1.09 ~ 1.37) 1.27 (1.13 ~ 1.43) 1.43 (1.23 ~ 1.66) 1.75 (1.31 ~ 2.33)	0.001 <0.001 <0.001 <0.001
Diabetic foot ulcer Event = 393 N = 11934	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	92 / 4443 108 / 3086 117 / 2788 65 / 1345 11 / 272		1 (Ref) 1.38 (1.04 ~ 1.83) 1.72 (1.30 ~ 2.28) 2.22 (1.60 ~ 3.07) 2.39 (1.27 ~ 4.49)	0.026 <0.001 <0.001 0.007
Chronic kidney disease Event = 1384 N = 10437	>=0 to <=20 >20 to <=40 >40 to <=60 >60 to <=80 >80 to <=100	356 / 3736 425 / 2597 398 / 2544 169 / 1277 36 / 283		1 (Ref) 1.49 (1.29 ~ 1.72) 1.60 (1.38 ~ 1.85) 1.47 (1.22 ~ 1.78) 1.77 (1.25 ~ 2.49)	<0.001 <0.001 <0.001 0.001
		0.	.50 1.0 2.0 4.0		

Figure S9. The sensitivity analysis using the standard deviation (SD) of the HbA1c levels in accordance with the HVS category

Outcomes	Categories	n / N		HR (95% CI)	P value
MACE					
Event = 2389 N = 17366	Category 1 Category 2 Category 3 Category 4 Category 5	697 / 5692 668 / 5051 672 / 4509 320 / 1922 32 / 192		1 (Ref) 0.85 (0.76 ~ 0.95) 0.95 (0.85 ~ 1.07) 1.30 (1.13 ~ 1.49) 1.93 (1.35 ~ 2.75)	0.004 0.382 <0.001 <0.001
All-cause mortality		1000 / 0500			
Event = 4090 N = 19883	Category 1 Category 2 Category 3 Category 4 Category 5	1208 / 6533 1111 / 5779 1143 / 5160 556 / 2201 72 / 210		1 (Ref) 0.87 (0.80 ~ 0.94) 1.00 (0.92 ~ 1.09) 1.39 (1.25 ~ 1.54) 2.69 (2.12 ~ 3.43)	0.001 0.981 <0.001 <0.001
Atherosclerotic cardiovascular death	1			= .	
Event = 892 N = 19746	Category 1 Category 2 Category 3 Category 4 Category 5	243 / 6468 231 / 5752 280 / 5133 122 / 2183 16 / 210		1 (Ref) 0.80 (0.66 ~ 0.96) 1.05 (0.88 ~ 1.27) 1.34 (1.07 ~ 1.67) 2.78 (1.67 ~ 4.64)	0.017 0.585 0.012 <0.001
Coronary artery disease					
Event = 2228 N = 16413	Category 1 Category 2 Category 3 Category 4 Category 5	646 / 5386 635 / 4780 632 / 4228 279 / 1830 36 / 189		1 (Ref) 0.80 (0.71 ~ 0.90) 0.86 (0.76 ~ 0.97) 1.08 (0.93 ~ 1.25) 2.27 (1.62 ~ 3.18)	<0.001 0.012 0.302 <0.001
Ischemic stroke					
Event = 1136 N = 18609	Category 1 Category 2 Category 3 Category 4 Category 5	376 / 6086 319 / 5397 295 / 4851 134 / 2070 12 / 205		1 (Ref) 0.78 (0.67 ~ 0.91) 0.81 (0.69 ~ 0.95) 1.03 (0.84 ~ 1.27) 1.30 (0.73 ~ 2.32)	0.002 0.011 0.759 0.371
Heart failure					
Event = 853 N = 19059	Category 1 Category 2 Category 3 Category 4 Category 5	245 / 6286 248 / 5538 228 / 4932 121 / 2093 11 / 210		1 (Ref) 0.93 (0.77 ~ 1.12) 0.97 (0.80 ~ 1.18) 1.47 (1.17 ~ 1.84) 2.02 (1.10 ~ 3.70)	0.439 0.782 0.001 0.024
Diabetic retinopathy					
Event = 414 N = 15067	Category 1 Category 2 Category 3 Category 4 Category 5	52 / 5079 116 / 4462 157 / 3752 84 / 1605 5 / 169		1 (Ref) 1.21 (0.86 ~ 1.69) 1.60 (1.15 ~ 2.23) 2.63 (1.84 ~ 3.78) 4 2.85 (1.13 ~ 7.19)	0.275 0.005 <0.001 0.026
Diabetic peripheral neuropathy					
Event = 2526 N = 13111	Category 1 Category 2 Category 3 Category 4 Category 5	668 / 4351 750 / 3885 707 / 3312 357 / 1394 44 / 169	= = == -=-	1 (Ref) 0.92 (0.82 ~ 1.02) 0.96 (0.85 ~ 1.07) 1.50 (1.31 ~ 1.71) 2.18 (1.60 ~ 2.96)	0.126 0.433 <0.001 <0.001
Diabetic foot ulcer					
Event = 468 N = 15913	Category 1 Category 2 Category 3 Category 4 Category 5	89 / 5253 134 / 4731 155 / 4055 82 / 1694 8 / 180		1 (Ref) 1.10 (0.83 ~ 1.45) 1.37 (1.04 ~ 1.82) 2.29 (1.67 ~ 3.13) ∃ 3.56 (1.72 ~ 7.37)	0.519 0.026 <0.001 0.001
Chronic kidney disease					
Event = 1722 N = 13812	Category 1 Category 2 Category 3 Category 4 Category 5	411 / 4160 510 / 3904 511 / 3809 254 / 1734 36 / 205		1 (Ref) 0.91 (0.80 ~ 1.05) 0.96 (0.84 ~ 1.10) 1.36 (1.15 ~ 1.60) 2.48 (1.76 ~ 3.49)	0.190 0.567 <0.001 <0.001
		0.	.501.0 2.0 4.0		

Figure S10. The sensitivity analysis using the coefficients of variance (CV) of the HbA1c levels in accordance with the HVS category

Outcomes	Categories	n / N		HR (95% CI)	P value
MACE Event = 2389 N = 17366	Category 1 Category 2 Category 3 Category 4 Category 5	695 / 5693 677 / 5050 668 / 4510 320 / 1921 29 / 192		1 (Ref) 0.85 (0.76 ~ 0.95) 0.91 (0.82 ~ 1.02) 1.20 (1.05 ~ 1.38) 1.69 (1.17 ~ 2.46)	0.005 0.123 0.008 0.006
All-cause mortality Event = 4090 N = 19883	Category 1 Category 2 Category 3 Category 4 Category 5	1174 / 6533 1105 / 5779 1159 / 5160 584 / 2201 68 / 210	H. H. H.	1 (Ref) 0.89 (0.82 ~ 0.97) 1.01 (0.93 ~ 1.10) 1.39 (1.25 ~ 1.54) 2.47 (1.93 ~ 3.15)	0.007 0.823 <0.001 <0.001
Atherosclerotic cardiovascular death Event = 892 N = 19746	Category 1 Category 2 Category 3 Category 4 Category 5	241 / 6468 237 / 5752 282 / 5133 119 / 2183 13 / 210		1 (Ref) 0.82 (0.68 ~ 0.99) 1.04 (0.86 ~ 1.25) 1.19 (0.95 ~ 1.50) 2.12 (1.21 ~ 3.72)	0.034 0.709 0.127 0.008
Coronary artery disease Event = 2228 N = 16413	Category 1 Category 2 Category 3 Category 4 Category 5	638 / 5385 649 / 4781 637 / 4228 272 / 1830 32 / 189		1 (Ref) 0.82 (0.73 ~ 0.92) 0.85 (0.75 ~ 0.95) 0.98 (0.85 ~ 1.14) 1.95 (1.37 ~ 2.79)	<0.001 0.006 0.840 <0.001
Ischemic stroke Event = 1136 N = 18609	Category 1 Category 2 Category 3 Category 4 Category 5	377 / 6085 318 / 5398 288 / 4851 141 / 2070 12 / 205		1 (Ref) 0.77 (0.66 ~ 0.90) 0.76 (0.64 ~ 0.89) 1.01 (0.83 ~ 1.23) 1.32 (0.74 ~ 2.34)	0.001 0.001 0.934 0.350
Heart failure Event = 853 N = 19059	Category 1 Category 2 Category 3 Category 4 Category 5	242 / 6286 250 / 5538 233 / 4932 115 / 2093 13 / 210		1 (Ref) 0.96 (0.80 ~ 1.15) 0.97 (0.80 ~ 1.18) 1.28 (1.02 ~ 1.61) 2.56 (1.46 ~ 4.48)	0.660 0.772 0.034 0.001
Diabetic retinopathy Event = 414 N = 15067	Category 1 Category 2 Category 3 Category 4 Category 5	60 / 5079 131 / 4462 162 / 3752 58 / 1605 3 / 169		1 (Ref) 1.13 (0.82 ~ 1.54) 1.34 (0.98 ~ 1.84) 1.52 (1.04 ~ 2.20) 1.37 (0.43 ~ 4.39)	0.462 0.066 0.029 0.599
Diabetic peripheral neuropathy Event = 2526 N = 13111	Category 1 Category 2 Category 3 Category 4 Category 5	671 / 4351 765 / 3885 716 / 3312 332 / 1394 42 / 169	= -= -=-	1 (Ref) 0.92 (0.83 ~ 1.03) 0.93 (0.83 ~ 1.04) 1.30 (1.13 ~ 1.48) 1.95 (1.42 ~ 2.67)	0.154 0.180 <0.001 <0.001
Diabetic foot ulcer Event = 468 N = 15913	Category 1 Category 2 Category 3 Category 4 Category 5	92 / 5253 138 / 4731 168 / 4055 63 / 1694 7 / 180		1 (Ref) 1.07 (0.81 ~ 1.40) 1.38 (1.05 ~ 1.81) 1.59 (1.14 ~ 2.21) 2.70 (1.25 ~ 5.84)	0.641 0.022 0.006 0.012
Chronic kidney disease Event = 1722 N = 13812	Category 1 Category 2 Category 3 Category 4 Category 5	412 / 4160 492 / 3904 525 / 3809 264 / 1734 29 / 205		1 (Ref) 0.89 (0.77 ~ 1.02) 0.95 (0.83 ~ 1.09) 1.32 (1.12 ~ 1.55) 1.78 (1.22 ~ 2.60)	0.084 0.487 0.001 0.003
		(0.50 1.0 2.0 4.0		

Visit-to-visit HbA1c variability is associated with cardiovascular disease and microvascular complications in patients with newly diagnosed type 2 diabetes

Running Title: HbA1c variability and complications in diabetes

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Abstract

Objective: To investigate the association between visit-to-visit HbA1c variability and cardiovascular events and microvascular complications in patients with newly diagnosed type 2 diabetes.

Research Design and Methods: This retrospective cohort study analyzed patients from Tayside and Fife in the Scottish Care Information-Diabetes Collaboration (SCI-DC), who were observable from the diagnosis of diabetes and had at least five HbA1c measurements before the outcomes being evaluated. We used the previously reported HbA1c variability score (HVS) calculated as the percentage of the number of changes in HbA1c over 0.5% (5.5 mmol/mol) among all HbA1c measurement within an individual. The association between HVS and ten outcomes was assessed using Cox proportional-hazards models.

Results: We included 13,111 to 19,883 patients in the analyses of each outcome. The patients with HVS over 60% were associated with elevated risks of all outcomes compared with the lowest quintile (for example, hazard ratios and 95% confidence intervals [HVS >80 to ≤ 100 vs. HVS ≥ 0 to ≤ 20]: 2.38 [1.61~3.53] for major adverse cardiovascular events [MACE]; 2.4 [1.72~3.33] for all-cause mortality; 2.4 [1.13~5.11] for atherosclerotic cardiovascular [ASCV] death; 2.63 [1.81~3.84] for coronary artery disease; 2.04 [1.12~3.73] for ischemic stroke; 3.23 [1.76~5.93] for heart failure; 7.4 [3.84~14.27] for diabetic retinopathy; 3.07 [2.23~4.22] for diabetic peripheral neuropathy; 5.24 [2.61~10.49] for diabetic foot ulcer; 3.49 [2.47~4.95] for the newonset chronic kidney disease). Four sensitivity analyses, including adjustment for time-weighted average HbA1c confirmed the robustness of the results.

Conclusions: Our study shows that higher HbA1c variability is associated with increased risks of all-cause mortality, cardiovascular events and microvascular complication of diabetes independently of high HbA1c.

Keywords: HbA1c variability, cardiovascular event, all-cause mortality, heart failure, diabetic retinopathy, diabetic peripheral neuropathy, diabetic foot ulcer, chronic kidney disease

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Introduction

Although there is considerable evidence that intensive blood glucose normalization reduces the risk of both cardiovascular events and microvascular complications of diabetes (1-3), the effects were heterogeneous between trials. For example, the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial was terminated prematurely due to significantly elevated mortality and cardiovascular events (4), suggesting that the near-normalization of blood glucose should not be the only target of diabetes treatment. Glycemic variability is one factor that may explain these differences in cardiovascular outcomes.

Glycemic variability can be measured as either the glucose fluctuation within a day or the long-term visit-to-visit variability. The latter has been recently investigated in several studies, although the metrics and definition of the variability measure were inconsistent (5). Most studies evaluating HbA1c variability using the standard deviation (SD) or the coefficient of variation (CV) of HbA1c, suggested that these measures were associated with all-cause mortality and the development of the adverse outcomes of diabetes, after adjusting for the average HbA1c (6-11). However, neither SD or CV of HbA1c can be easily interpreted in clinical practice. Recently, Forbes and colleagues (12) developed a new scale, namely the HbA1c variability score (HVS) in the current study, to define the HbA1c variability. The HVS indicates how frequently the HbA1c rises or decreases by more than 0.5% (5.5mmol/mol), which is in line with the SD and CV of HbA1c but clinically more translatable (as it can be interpreted as the percentage of total HbA1c measures that vary by more than 0.5% or 5.5mmol/mol) (6,12). However, the HVS has not been widely used among the studies of HbA1c variability, with previous studies using this scale only focusing on the elderly and non-diabetic population and evaluating mainly mortality as an outcome (6,12). It is unclear whether HVS is associated with microvascular complications of diabetes and whether the increased cardiovascular risk described could be extended to real-world patients with type 2 diabetes. In this study we aimed to investigate the association between visit-to-

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visit HbA1c variability and both cardiovascular diseases and microvascular complications in a large population database of patients with newly diagnosed type 2 diabetes.

Research Design and Methods

Data source and study population

The population was selected from patients from Tayside and Fife in the Scottish Care Information-Diabetes Collaboration (SCI-DC), the electronic health record system used in Scotland for patients with diabetes. The patients were included if they: 1) were diagnosed with type 2 diabetes; 2) had their first HbA1c measurement within one year from diagnosis of diabetes; 3) were over 40 years old when first diagnosed with diabetes; 4) did not experience any study outcome before or within three years since diagnosis of diabetes; 5) had at least five records of HbA1c measurement between diagnosis of diabetes and the first episode of the study outcome. Patients were excluded where data were incomplete (details see the **Supplementary Techniques**). Data provision and linkage were carried by the University of Dundee Health Informatics Centre (HIC, https://www.dundee.ac.uk/hic), with analyses of anonymized data performed in an ISO27001 and Scottish Government accredited secure safe haven. HIC Standard Operating Procedures have been reviewed and approved by the NHS East of Scotland Research Ethics Service and consent for this study was obtained from the NHS Fife Caldicott Guardian.

Baseline parameters and follow-up

The body mass index (BMI), estimated glomerular filtration rate (eGFR), smoking status at baseline were captured from the medical record within one year from the diagnosis of diabetes (details see the **Supplementary Techniques**). The follow-up was defined by the first event of outcome or the last measurement of HbA1c before 24 April 2017 in the event-free case. Charlson Co-morbidity Index (CCI) was calculated using

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the ICD (International Classification of Diseases)-9 and ICD-10 code within the year after the diagnosis of diabetes (13), while we specifically removed the items of diabetes and cardiovascular events, which were overlapping with our population or outcomes.

Assessment of visit-to-visit HbA1c variability

To avoid the interaction between the HbA1c variability parameter with the frequency of HbA1c measurement and to better fit clinical practice, the HbA1c variability was evaluated using HVS, which was adopted from a recent publication (12). Briefly, HVS is the number of measures within an individual where the HbA1c has changed by > 0.5% (5.5mmol/mol) from the value prior, as a percentage of the total number of HbA1c measures between the diagnosis of diabetes and the outcome of interest for that individual (**Fig. S1**). To avoid the impact of multiple HbA1c measures in a short space of time, we allocated one HbA1c measure for every three-month period, using the median of all the HbA1c measures within that time. The resulting variability measure is termed the binned HVS (b-HVS). We also calculated the time-weighted average HbA1c, which was calculated using the area under the curve (AUC) of HbA1c from the diagnosis of diabetes to the first event divided by the duration.

Outcomes

We examined ten outcomes of interest including: major adverse cardiovascular events (MACE); all-cause mortality; atherosclerotic cardiovascular death (ASCV death); hospitalization or death from coronary artery disease, ischemic stroke or heart failure; observable background diabetic retinopathy (DR), diabetic peripheral neuropathy (DPN); diabetic foot ulcer (DFU); and the new onset of chronic kidney diseases (CKD). If the event of interest occurred within the first three years from the diagnosis of diabetes, the patient was excluded from the analysis of that outcome, to avoid the outcome occurring close to diagnosis before the HVS could be defined, when the outcome would be unlikely to be related to the HVS. For full definitions of the endpoints (see the **Supplementary Techniques**).

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Statistical Analyses

The categorical variables were described using frequency and percentage. The continuous variables were described using means and SDs if normally distributed or median interquartile range (IQR) if not. Cox proportional-hazards model was used to assess the association between the HbA1c variability and each of the outcomes. The association of the adverse outcome with the HVS categories (≥ 0 to ≤ 20 , ≥ 20 to ≤ 40 , ≥ 40) to ≤ 60 , > 60 to ≤ 80 , > 80, with the ≥ 0 to ≤ 20 as reference) were adjusted for sex, index age, calendar year, Scottish Index of Multiple Deprivation (SIMD) quintiles, ever smoking, hypertension at baseline, BMI at baseline, high-density lipoprotein (HDL) cholesterol at baseline, eGFR at baseline, antiplatelet therapy at baseline and CCI (≥1 vs 0). We used Survival::cox.zph Pack in R to test the proportional hazards assumption for Cox regression models (14) for all our models. We considered the proportional hazards assumptions to be violated if the global P-value lower than 0.01. Because of the violation of proportional hazards assumptions the stage of CKD (stage 1 or 2) at baseline rather than the eGFR at baseline was stratified in the analysis of the new onset of the CKD. Five subgroup analyses were introduced based on the age (<65 years vs \geq 65 years), sex, BMI at baseline (>30kg/m² vs \leq 30kg/m²), time-weighted mean HbA1c (>7% vs <27% or >53mmol/mol vs <53mmol/mol), and treatment at baseline (medication/insulin-treated vs. lifestyle intervention only). Five sensitivity analyses were performed for each outcome by: 1) adjusting for time-weighted average HbA1c; 2) using the b-HVS instead of HVS; 3) using the HVS based on the HbA1c measurement solely focusing on the first three years after diagnosis of diabetes, prior to the occurrence of any event; 4) using the individual-level SDs of the HbA1c instead of the HVS; 5) using individual-level CVs of HbA1c instead of the HVS. Analyses were undertaken in the SAS® 9.4 (SAS Institute Inc., Cary, NC, USA). and the RStudio for Windows (R version 3.2.5).

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Results

Baseline characteristics

As shown in **Fig. 1**, among the 79,569 patients with type 2 diabetes identified in the population, we included 21,352 patients for further analysis., The average age was 63.3 \pm 11.1 years when recruited and 54.6% of them were male. The median follow-up duration was 6.8 (IQR: 4.6~11.2) years. The mean HbA1c at baseline was 7.7% \pm 2.0% (60.7 \pm 21.4 mmol/mol), and the median number of HbA1c measurements throughout the study period was 12 (IQR: 8~19) times during the follow-up duration. **Tab. S1** shows the baseline patient characteristics for those included for each analysis of outcomes and **Tab. 1** shows how the baseline characteristics differ across the HVS categories. 62% of the patients have an HVS below or equal to 40%; 12.5% have an HVS greater than 60%. As expected, an increasing HVS is associated with younger age of diagnosis, higher BMI, and more intensive diabetes treatment including greater insulin use.

HbA1c variability and outcomes

As shown in **Fig. 2**, between 13,111 to 19,883 patients were involved in the analyses of each outcome. Comparing with the reference (lowest HVS category, ≥ 0 to ≤ 20), patients with HVS over 60 were associated with increased risks of all outcomes in a fully adjusted Cox model. For example, those with HVS >80 to ≤ 100 had an increased risk of (HR [95%CI]): MACE: 2.38 [1.61~3.53]; all-cause mortality: 2.4 [1.72~3.33]; ASCV death: 2.4 [1.13~5.11]; coronary artery disease: 2.63 [1.81~3.84]; ischemic stroke: 2.04 [1.12~3.73]; heart failure: 3.23 [1.76~5.93]; DR: 7.4 [3.84~14.27]; DPN: 3.07 [2.23~4.22]; DFU: 5.24 [2.61~10.49]; CKD: 3.49 [2.47~4.95]).

Subgroup analyses and sensitivity analyses

Given the association between HVS and HbA1c we first undertook a sensitivity analysis, including time-weighted average HbA1c from diagnosis to event in the models (Fig. 3). The results were similar for most outcomes other than retinopathy where the

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association of HVS was diminished when adjusting for the time-weighted average HbA1c.

When comparing the subgroups with time-weighted average HBA1c more than or less than 7% (53mmol/mol) there was a stronger association between the HVS and coronary artery disease, ischemic stroke and progression to CKD in patients with time-weighted average HbA1c<7% or 53mmol/mol (**Fig. S5**). Other subgroup analyses were undertaken based on age (**Fig. S2**), sex (**Fig. S3**), obesity at baseline (**Fig. S4**) and treatment at baseline (**Fig. S6**) did not show significant differences in the trend of the association (except the cases with very small sample size). Using b-HVS instead of HVS also showed consistent results in all outcomes (**Fig. S7**). However, the sensitivity analysis using the first-three year HVS suggested a weaker association compared with the main analysis (**Fig. S8**). The sensitivity analysis using the individual-level SD (**Fig. S9**) and CV (**Fig. S10**) of HbA1c showed a similar pattern of risk for most outcomes but not ischemic stroke for SD and CV and diabetic retinopathy for CV where weaker associations were observed.

Discussion

To our knowledge, this is the first population-based study to investigate the association between the visit-to-visit HbA1c variability and comprehensive endpoints including cardiovascular events and the microvascular complications of diabetes in patients with newly diagnosed type 2 diabetes independent of the time-weighted average HbA1c.

Our study showed clear elevated risks of adverse events in the ~12.5% of patients with a HVS higher than 60 (meaning those with 60% of their HbA1c measurements increased or decreased by > 0.5% (5.5mmol/mol) compared with the last measurement) after diagnosis of diabetes adjusted for their time-weighted average HbA1c. The results were consistent with previous studies based on trial (15,16) and observational datasets (6-12,17). Our results indicate that frequent fluctuations of HbA1c of patients with

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diabetes may be an independent risk factor of poor prognosis and more stable HbA1c control may benefit the patients in clinical practice, although it should be emphasized that our results are observational and causal inference cannot be made. Of note, a recent analysis based on the VADT trial (16) suggested that higher HbA1c variability was associated with the increased risk of cardiovascular events in the group of intensive glycemic control but not the standard control. It suggested that the increased HbA1c variability may neutralize the cardiovascular benefits of the sustained 1.5% (16.4 mmol/mol) HbA1c reduction during the study period (18). We undertook a subgroup analysis looking at HVS in those with good and poor average HbA1c. It was interesting to note that the HVS association with atherosclerotic cardiovascular events was greater in those with good HbA1c, in keeping with the VADT finding. However, we need to interpret these results with caution as we can not account for treatment intensity during the study period.

We have previously reported that patients with high variability in HbA1c have high cardiovascular risk at baseline (19), and thus the association of HbA1c variability with risk may not be a feature of the HbA1c variability per se, but a marker of this baseline difference in patient characteristics. In this current study we have adjusted comprehensively for baseline differences in cardiovascular risk although we acknowledge there could be residual confounding. It is interesting to note that in the sensitivity analysis where we restrict our analysis to defining HbA1c variability only on the first three years of HbA1c measures, the association with micro- and macrovascular outcomes are diminished. This suggests that the HbA1c variability may continuously contribute to the clinical adverse endpoints beyond the first three years, and therefore that the risk can be less attributable to baseline differences in patient characteristics and more attributable to the HbA1c variability per se. As a recent study suggested that HbA1c variability is associated with the quality of patient care (20), it also suggests that it is never too late to reduce the HbA1c variability in clinical practice.

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Although infeasible in the current analysis, it would also be interesting to evaluate HbA1c variability on different anti-diabetic treatments to see if reduced variability can explain some of the improved outcomes with some of these agents.

Although we cannot attribute poor prognosis to the HbA1c variability per se, some underlying mechanisms may explain the association observed in our study. Although oxidative stress is suggested to be the explanation between short-term glycemic variability and adverse outcomes (5), it is not clear whether this is increased in patients with high visit-to-visit HbA1c variability. An alternative may relate to accumulated epigenetic modification induced by both high and low glycemia (21). Another explanation may simply relate to increased hypoglycemia in these individuals, since some studies suggest high HbA1c variability is linked to increased risk of severe hypoglycemic episodes (22) and patients admitted to hospital due to hypoglycemia have higher HbA1c variability (23). It will be valuable if a further study could address the frequency of overall and severe hypoglycemia among patients with different HbA1c variability.

The strengths of our study are clear. Firstly, all the included patients were tracked with their HbA1c measurement from the diagnosis of diabetes, so there is no period of the patients' diabetes journey that is not captured. Secondly, we comprehensively studied ten clinically important outcomes, including all-cause mortality, cardiovascular events and major microvascular complications of diabetes and showed consistent results across these micro- and macrovascular endpoints. Thirdly, our results were confirmed by a series of subgroup analyses and sensitivity analyses including adjusting for the time-weighted average HbA1c from the diagnosis of diabetes. Fourthly, our study was based on the real-world data of diabetes care in Scotland making these results directly translatable to clinical practice. Finally, we have used the HVS rather than SD or CV which we feel is much more clinically tractable. Although SD and CV reflect the dispersion trend of the HbA1c measures in an individual, they are no more than

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clinically meaningless statistical parameters. When considering the HVS, the clinicians can review the HbA1c profile for an individual – those where more than 60% of measures vary by more than 0.5% are at high risk.

The study does have limitations. Firstly, as a retrospective cohort study, uncorrected confounding could be possible and individuals with higher HbA1c variability may also at higher cardiovascular risks of other causes (18), and we cannot conclude an association of variability per se with the outcomes. Nevertheless, we used Cox proportional-hazards models to minimize the possible known confounding factors including CCI, smoking status and social deprivation and used a series of subgroup analyses and sensitivity analyses to confirm our findings to be robust. Secondly, we did not adjust for or evaluate the contribution of hypoglycemia, which has been reported to be associated with HbA1c variability (15) in the association between the HbA1c variability and outcomes because of the limitation of the data. Thirdly, the median follow-up duration of the study was 6.8 years and this will limit the total incident outcomes. The need to only include patients with newly diagnosed diabetes and other inclusion criteria do limit the total follow up time in this study population. This relatively short median duration does reduce the number of long-term outcome events especially for retinopathy and diabetic foot ulcer. Studies with longer follow-up duration in larger populations would be of value.

Conclusion

In conclusion, our study shows that higher HbA1c variability from the diagnosis of diabetes is independently associated with increased risks of all-cause mortality, major cardiovascular and microvascular complications of diabetes.

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Acknowledgment

SL, KZ and ERP conceived the study. SL, IN, LD and SH performed the statistical analyses. SL and ERP drafted the manuscript. ERP takes responsibility for the contents of the article as the guarantor.

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Table and table legend

Table 1. Baseline characteristics of the overall study population

HVS Scores	≥0 to ≤20	>20 to ≤40	>40 to ≤60	>60 to ≤80	>80
n	7,084	6,096	5,502	2,409	261
Age of diabetes diagnosis, yrs	67.1 ± 10.3	63.5 ± 10.5	60.5 ± 10.9	58.9 ± 11.2	57.5 ± 11.2
Sex (male), n (%)	3,569 (50.4)	3,305 (54.2)	3,179 (57.8)	1,446 (60.0)	165 (63.2)
SIMD quintile, n (%)					
Q1	1,251 (17.7)	1,165 (19.1)	1,171 (21.3)	503 (20.9)	62 (23.8)
Q2	1,263 (17.8)	1,134 (18.6)	1,121 (20.4)	471 (19.6)	51 (19.5)
Q3	1,328 (18.7)	1,175 (19.3)	1,016 (18.5)	493 (20.5)	52 (19.9)
Q4	1,936 (27.3)	1,629 (26.7)	1,409 (25.6)	634 (26.3)	60 (23.0)
Q5	1,306 (18.4)	993 (16.3)	785 (14.3)	308 (12.8)	36 (13.8)
Year of diabetes diagnosis [*]	2010 [2005,	2008 [2002,	2008 [2002,	2009 [2003,	2010 [2006,
	2012]	2011]	2011]	2011]	2013]
BMI, kg/m ²	31.3 ± 6.0	31.9 ± 6.2	32.8 ± 6.5	33.3 ± 7.1	33.2 ± 7.3
Ever smoking, n (%)	4,881 (68.9)	4,336 (71.1)	3,977 (72.3)	1,748 (72.6)	178 (68.2)
Ever regular alcohol, n (%)	4,008 (61.2)	3,345 (59.1)	2,875 (57.3)	1,185 (54.5)	131 (56.5)
Systolic blood pressure, mmHg	140.1 ± 19.0	141.2 ± 19.5	140.3 ± 19.8	139.6 ± 19.6	138.2 ± 19.4
Diastolic blood pressure, mmHg	78.9 ± 10.8	81.0 ± 10.9	82.2 ± 11.2	82.2 ± 11.4	82.2 ± 12.0
Carlson Comorbidity Index ≥1, n (%)	1,332 (18.8)	1,073 (17.6)	867 (15.8)	449 (18.6)	58 (22.2)
Hypertension, n (%)	5,505 (77.7)	4,376 (71.8)	3,786 (68.8)	1,574 (65.3)	155 (59.4)
Treatment of diabetes within the first year from the					
diagnosis of diabetes, n (%)					
Lifestyle intervention only	5,260 (74.3)	3,137 (51.5)	2,190 (39.8)	740 (30.7)	61 (23.4)
Anti-diabetic agents without insulin	1,770 (25.0)	2,821 (46.3)	3,153 (57.3)	1,569 (65.1)	188 (72.0)

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Treated with insulin	54 (0.8)	138 (2.3)	159 (2.9)	100 (4.2)	12 (4.6)
Receiving anti-platelet therapy, n (%)	2,465 (34.8)	1,909 (31.3)	1,598 (29.0)	667 (27.7)	67 (25.7)
Receiving statins, n (%)	4,866 (68.7)	3,716 (61.0)	3,218 (58.5)	1,373 (57.0)	161 (61.7)
HbA1c at baseline, %	6.7 ± 1.2	7.8 ± 1.9	8.4 ± 2.1	8.9 ± 2.3	9.6 ± 2.5
HbA1c at baseline, mmol/mol	49 ± 13.0	62 ± 20.3	68 ± 23.1	77.4 ± 24.6	81 ± 26.8
HDL cholesterol, mmol/L	1.3 ± 0.4	1.2 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3
Non-HDL cholesterol, mmol/L	3.5 ± 1.2	3.8 ± 1.2	3.9 ± 1.3	4.0 ± 1.3	4.0 ± 1.1
ALT, IU/L*	24 [18, 34]	28 [20, 39]	30 [21, 45]	32 [22, 48]	32 [22, 48]
eGFR, mL/min/1.73m ²	72.2 ± 18.7	73.7 ± 18.8	77.2 ± 19.1	80.7 ± 19.7	84.1 ± 20.8

* Presented as median [the interquartile range]

Abbreviations: ALT: alanine aminotransferase; BMI: body mass index; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein;

SIMD: Scottish Index of Multiple Deprivation

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Figures and figure legends

Figure 1. The flow diagram of the patient selection

Abbreviations: ASCV: atherosclerotic cardiovascular; CKD: chronic kidney diseases; CV: cardiovascular; DFU: diabetic foot ulcer; DPN: diabetic peripheral neuropathy; DR: diabetic retinopathy; MACE: major adverse cardiovascular events.

Figure 2. The association between HbA1c variability score and adverse

outcomes in patients with newly diagnosed type 2 diabetes

Abbreviations: CI: confidence interval; HR: hazard ratio.

Figure 3. The association between HbA1c variability score and adverse

outcomes in patients with newly diagnosed type 2 diabetes after adjusting for the time-weighted average HbA1c

Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.

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