

## SUPPLEMENTARY DATA

### Supplementary Techniques

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#### 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 high-density 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 1.73m<sup>2</sup> 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 diastolic blood pressure >90mmHg), or receiving at least two prescriptions of the anti-hypertensive drug (angiotensin-converting-enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, beta-blockers or non-dihydropyridine 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 1.73m<sup>2</sup>).

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

	<b>MACE (n = 17,366)</b>	<b>All-cause mortality (n = 19,883)</b>	<b>Cardiovascu lar death (n = 19,746)</b>	<b>Coronary artery disease (n = 16,413)</b>	<b>Ischemic stroke (n = 18,609)</b>	<b>Heart failure (n = 19,059)</b>	<b>Diabetic retinopathy (n = 15,067)</b>	<b>Diabetic peripheral neuropathy (n = 13,111)</b>	<b>Diabetic foot ulcer (n = 15,913)</b>	<b>Chronic kidney disease (n = 13,812)</b>
Age of diabetes diagnosis, yrs	62.7 ± 11.0	63.2 ± 11.0	63.1 ± 11.0	62.5 ± 11.0	62.9 ± 10.9	62.9 ± 10.9	62.8 ± 10.7	62.3 ± 10.6	63.0 ± 10.8	59.5 ± 9.8
Sex (male), n (%)	9,202 (53.0)	10,854 (54.6)	10,777 (54.6)	8,594 (52.4)	10,080 (54.2)	10,329 (54.2)	8,206 (54.5)	7,061 (53.9)	8,577 (53.9)	8,418 (60.9)
SIMD quintile, n (%)										
Q1	3,246 (18.7)	3,818 (19.2)	3,784 (19.2)	3,073 (18.7)	3,534 (19.0)	3,636 (19.1)	2,863 (19.0)	2,459 (18.8)	3,028 (19.0)	2,724 (19.7)
Q2	3,265 (18.8)	3,755 (18.9)	3,738 (18.9)	3,015 (18.4)	3,526 (18.9)	3,597 (18.9)	2,812 (18.7)	2,424 (18.5)	2,960 (18.6)	2,590 (18.8)
Q3	3,282 (18.9)	3,789 (19.1)	3,756 (19.0)	3,130 (19.1)	3,518 (18.9)	3,620 (19.0)	2,863 (19.0)	2,440 (18.6)	3,005 (18.9)	2,597 (18.8)
Q4	4,710 (27.1)	5,315 (26.7)	5,275 (26.7)	4,467 (27.2)	5,003 (26.9)	5,114 (26.8)	4,061 (27.0)	3,627 (27.7)	4,343 (27.3)	3,667 (26.5)
Q5	2,863 (16.5)	3,206 (16.1)	3,193 (16.2)	2,728 (16.6)	3,028 (16.3)	3,092 (16.2)	2,468 (16.4)	2,161 (16.5)	2,577 (16.2)	2,234 (16.2)
Year of diabetes diagnosis*	2009 [2003, 2011]	2009 [2003, 2011]	2009 [2003, 2011]	2009 [2003, 2011]	2009 [2003, 2011]	2009 [2003, 2011]	2008 [2003, 2010]	2006 [2002, 2010]	2006 [2002, 2010]	2009 [2004, 2011]
BMI, kg/m <sup>2</sup>	32.2 ± 6.4	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

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



## SUPPLEMENTARY DATA

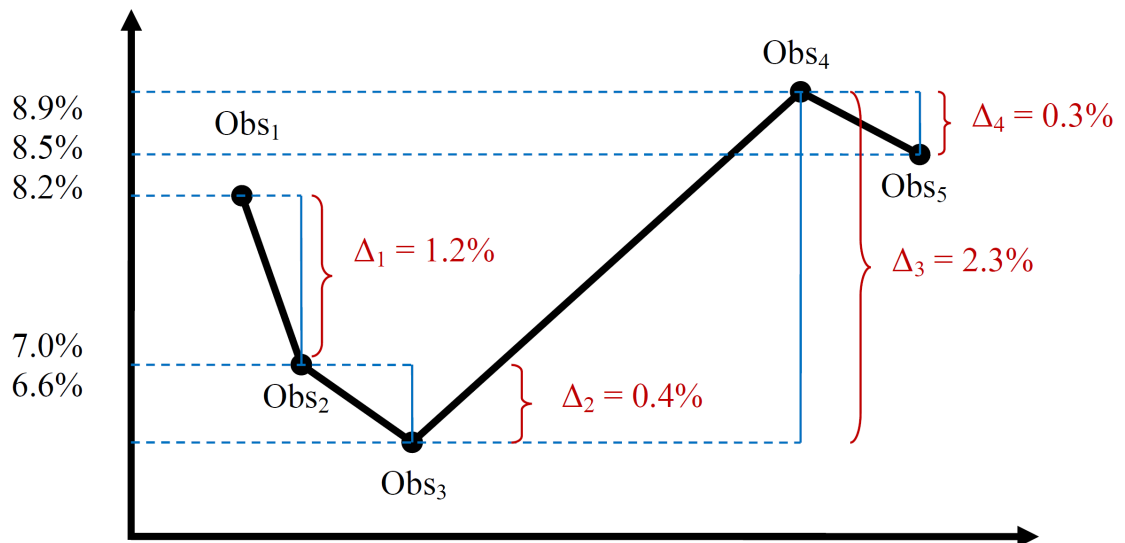
HbA1c, %	7.7 ± 2.0	7.7 ± 2.0	7.7 ± 2.0	7.8 ± 2.0	7.7 ± 2.0	7.7 ± 2.0	7.7 ± 2.0	7.8 ± 2.0	7.8 ± 2.0	7.8 ± 2.0
	2.0									
HbA1c, mmol/mol	61 ± 21.8	61 ± 21.6	61 ± 21.5	61 ± 22.0	61 ± 21.6	61 ± 21.5	61 ± 21.5	61 ± 22.1	61 ± 21.9	62 ± 22.0
HDL cholesterol, mmol/L	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3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

\* 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

SUPPLEMENTARY DATA

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

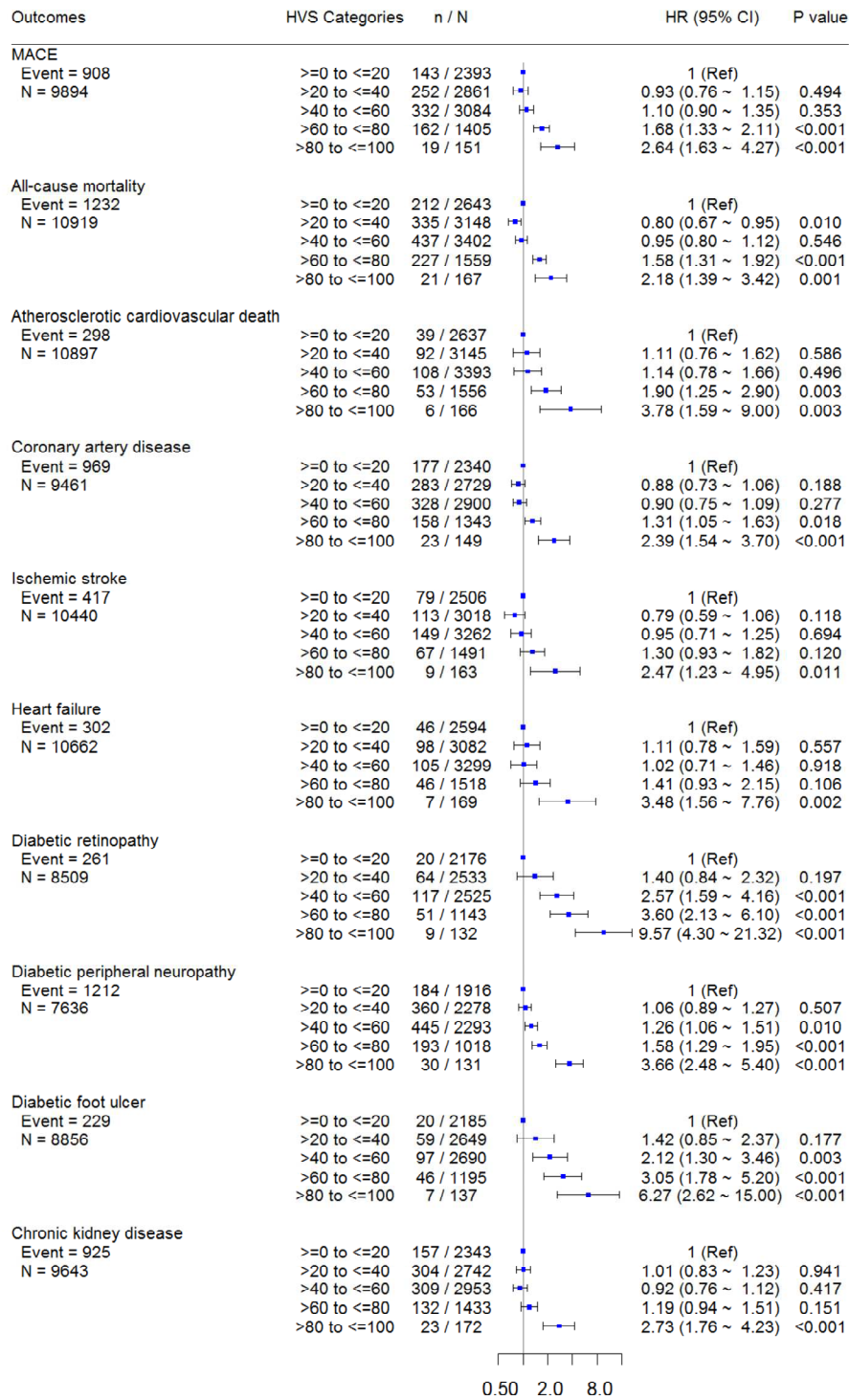


HbA1c Variability Score (HVS) = Number of HbA1c fluctuation events ( $\Delta > 0.5\%$ ) / (Total number of HbA1c measurements - 1)  $\times$  100  
In this case, there are 2 fluctuation events ( $\Delta_1$  &  $\Delta_3$ ) in 5 HbA1c measurements (4  $\Delta$ s).  $\therefore$  HVS =  $2 / (5 - 1) \times 100 = 50$

SUPPLEMENTARY DATA

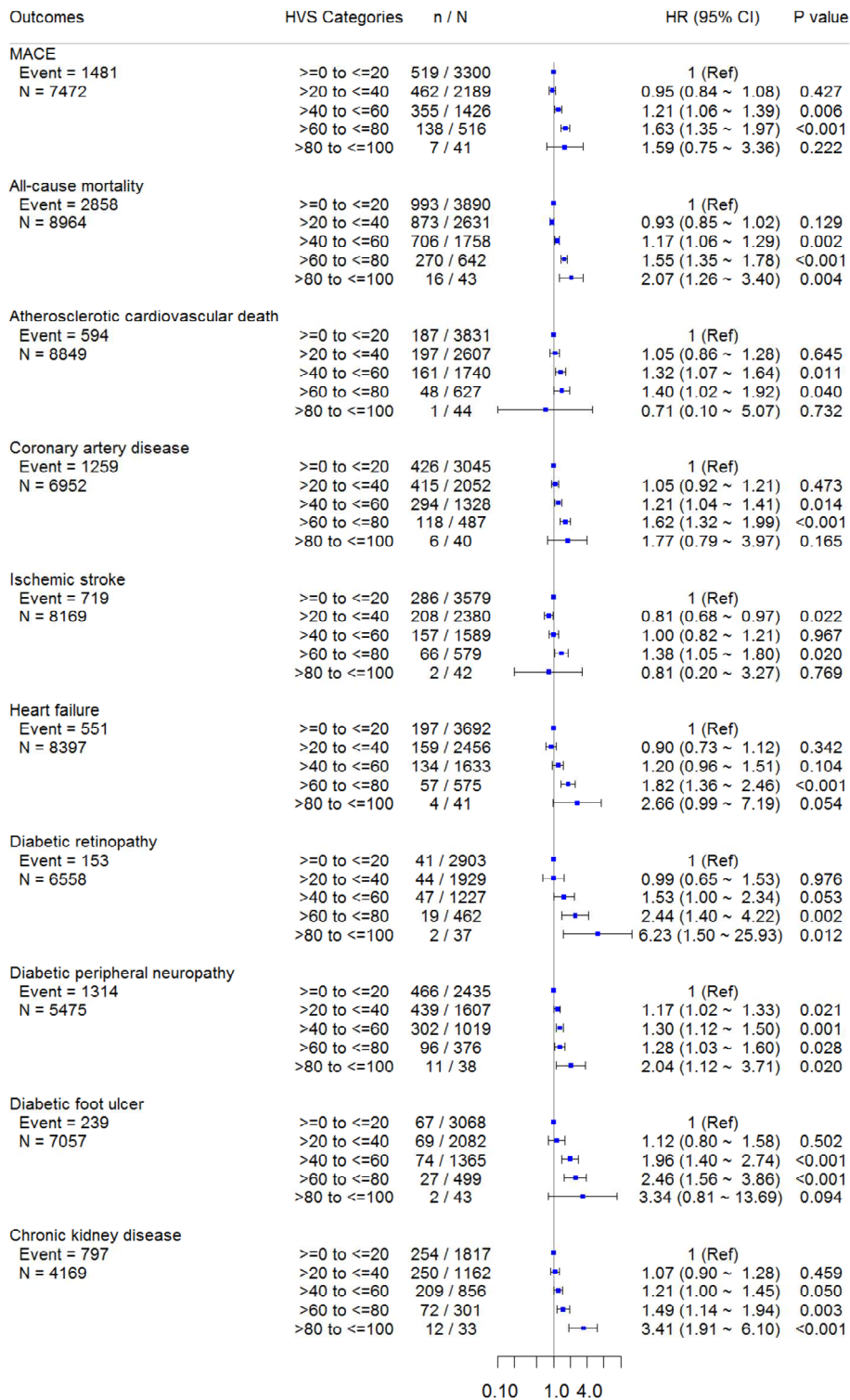
Supplementary Figure S2. The subgroup analysis based on the age

A.



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B.

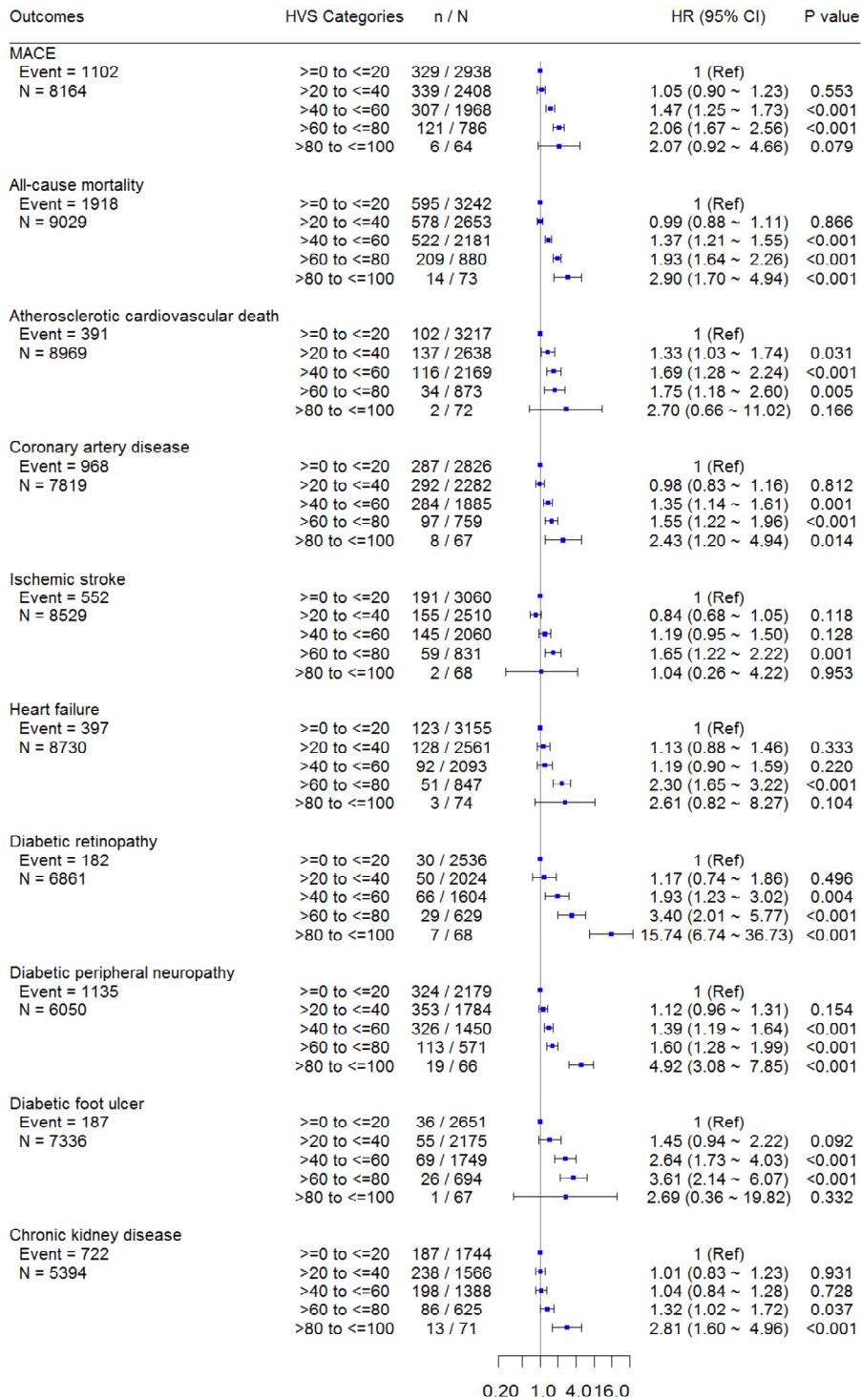


A. the subgroup of patients younger than 65; B. the subgroup of patients aged 65 or older  
Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.

SUPPLEMENTARY DATA

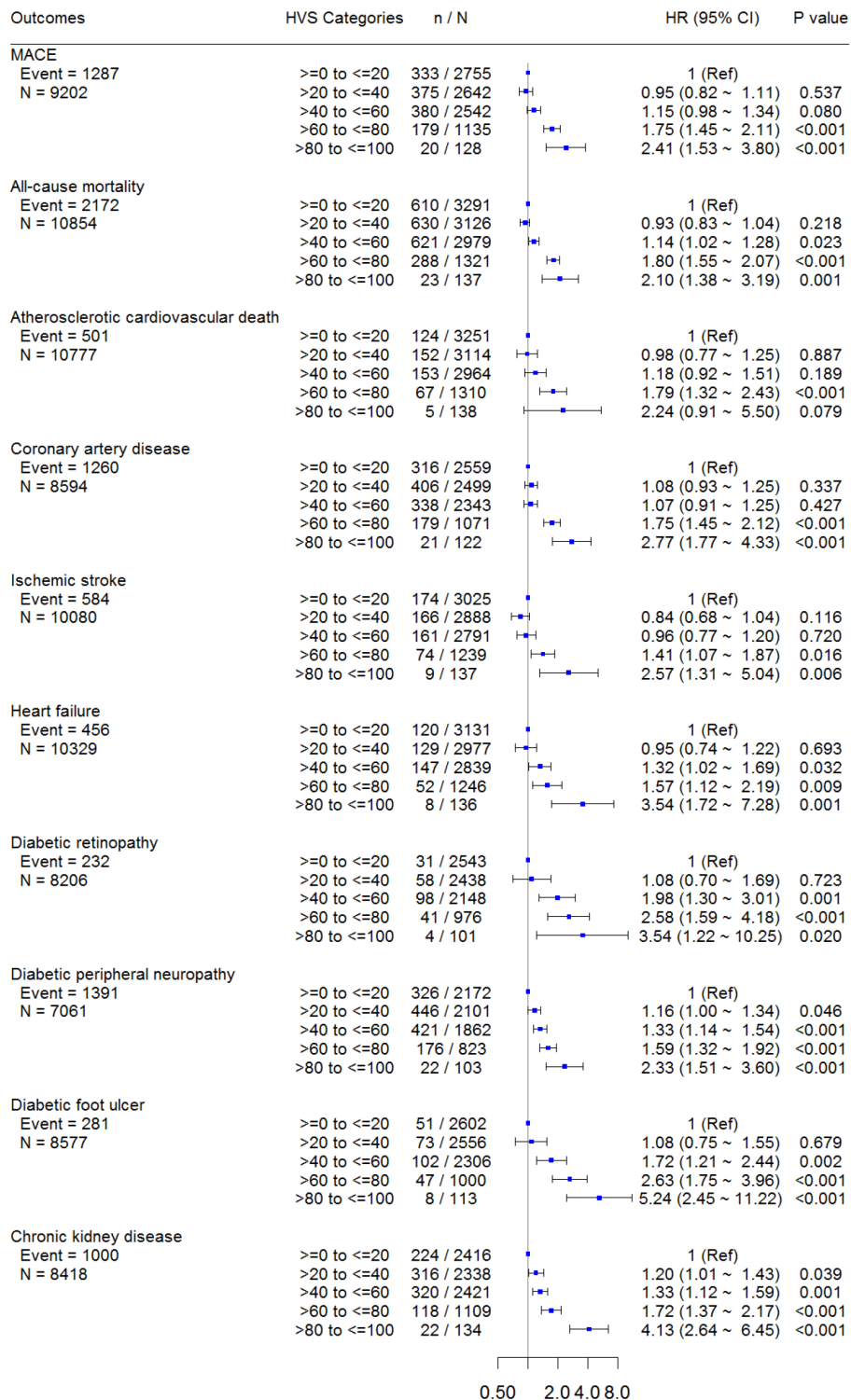
Supplementary Figure S3. The subgroup analysis based on sex

A.



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B.



A. the subgroup of female patients; B. the subgroup of male patients

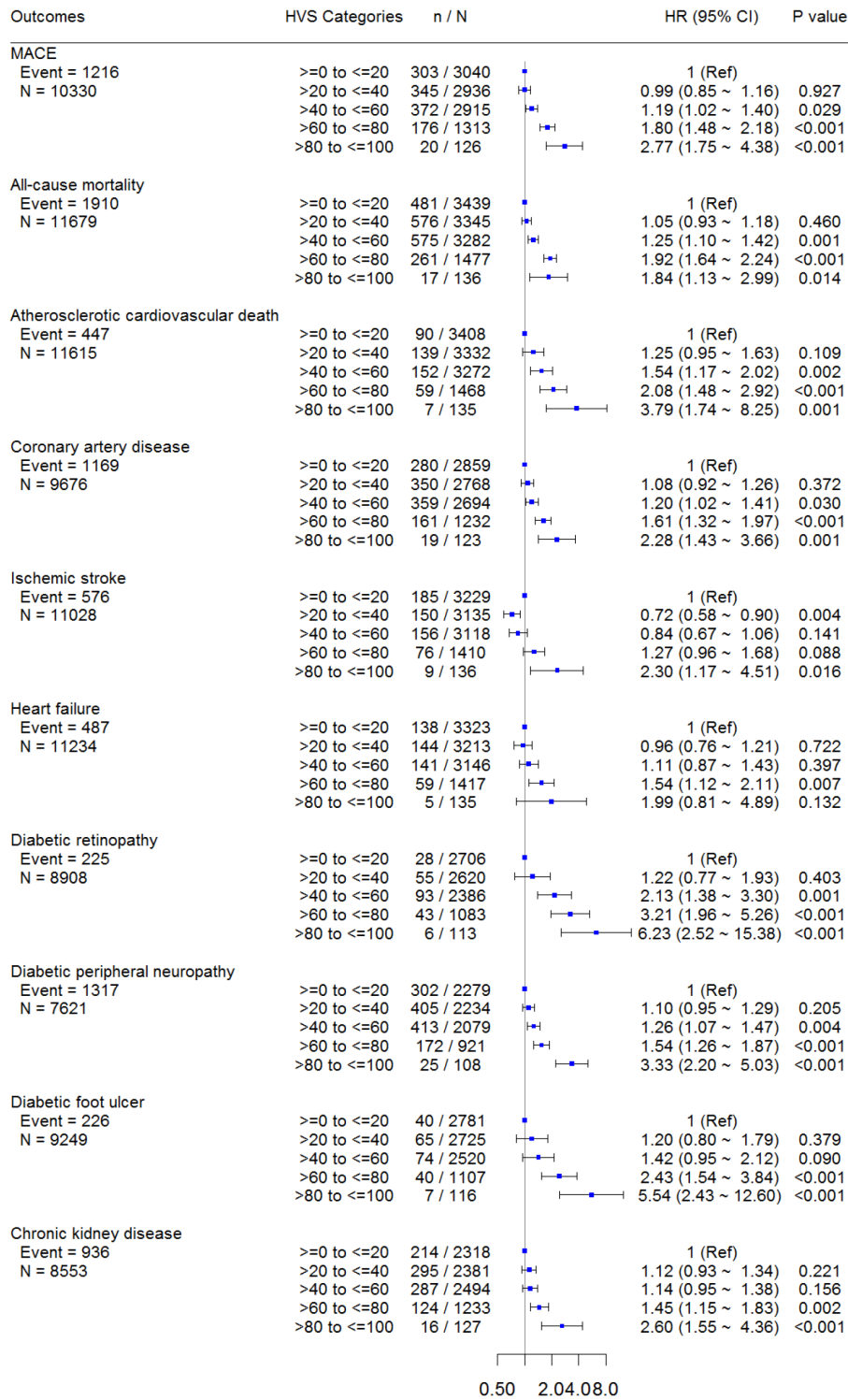
Abbreviations: CI: confidence interval; HR: hazard ratio.



SUPPLEMENTARY DATA

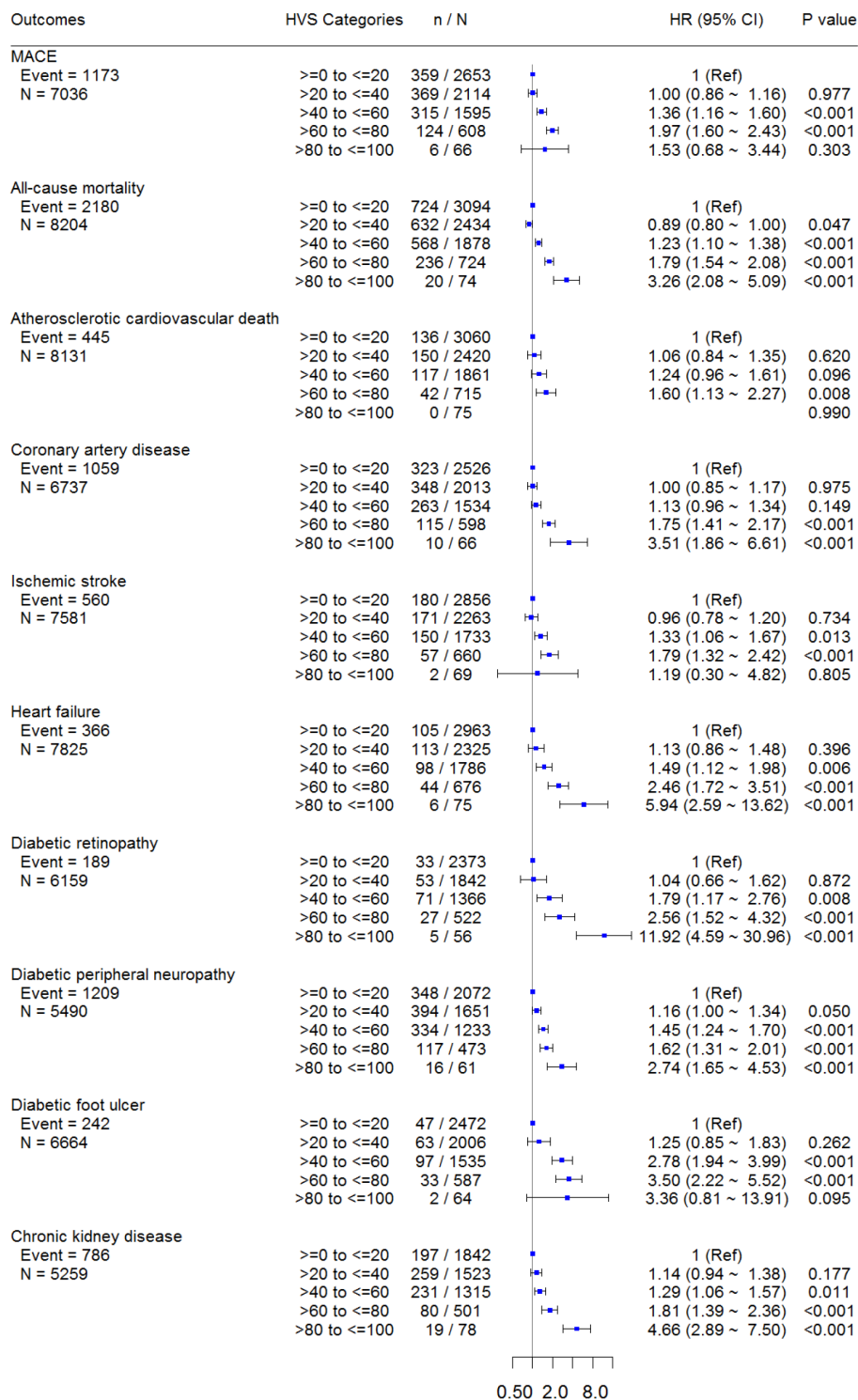
Supplementary Figure S4. The subgroup analysis based on the baseline body mass

A.



SUPPLEMENTARY DATA

B.



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

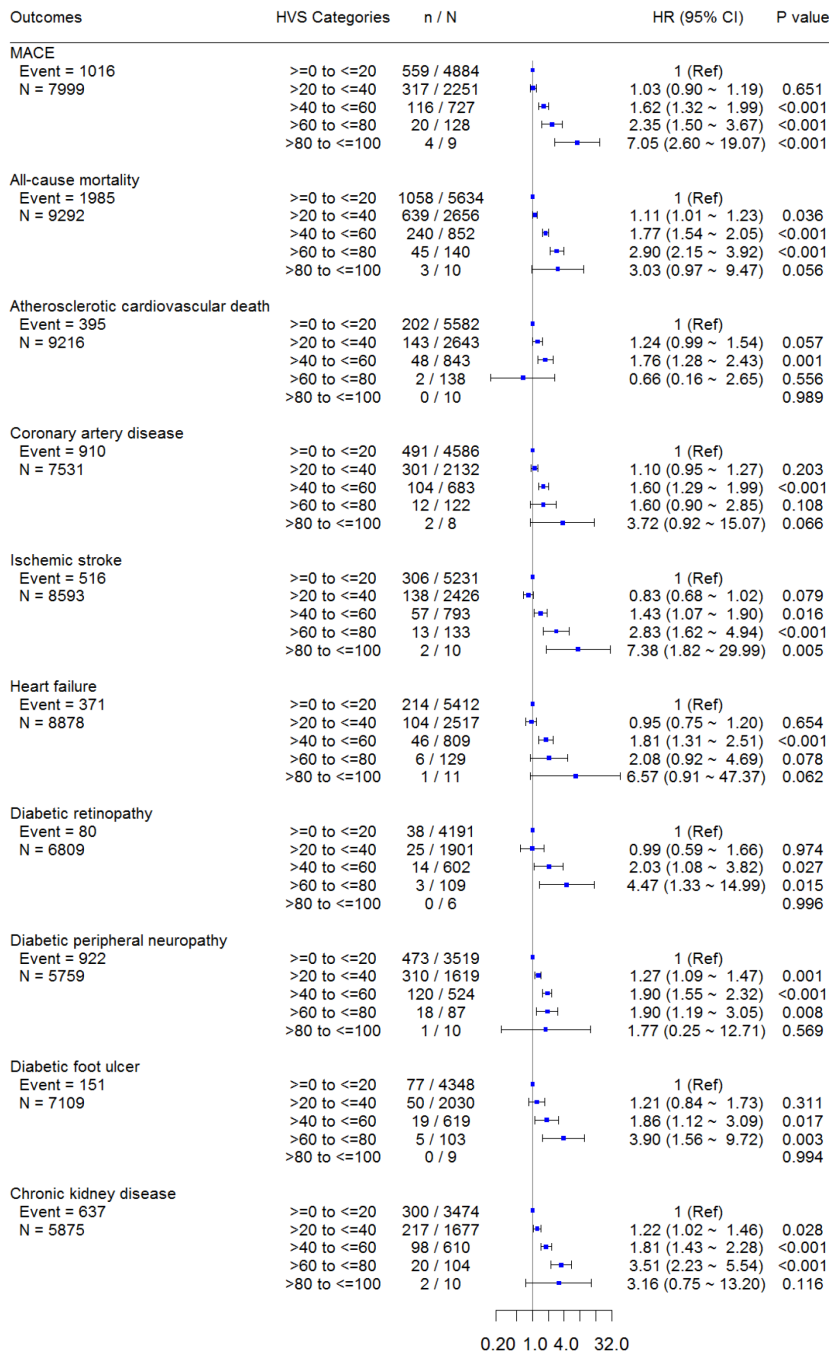
Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.



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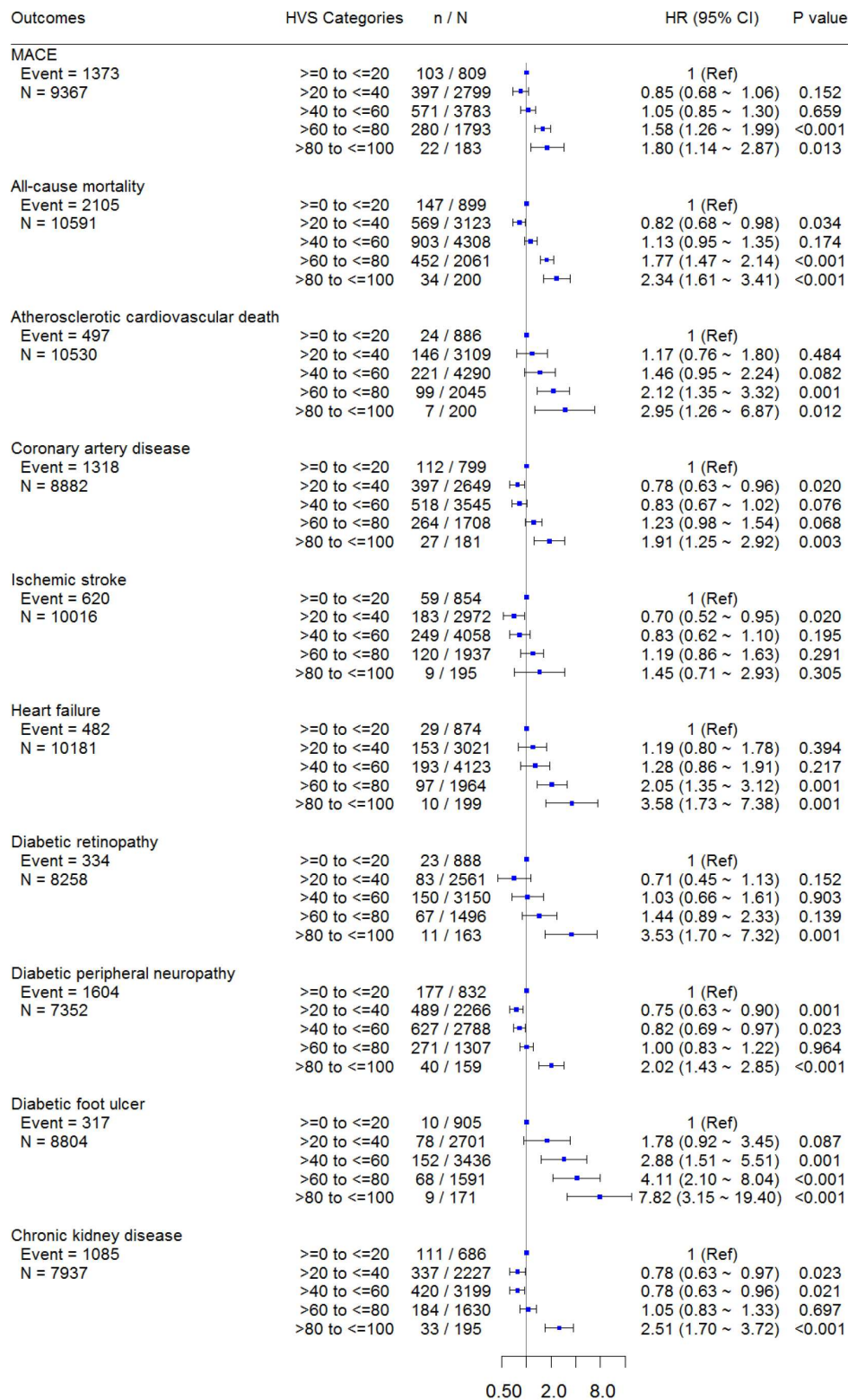
Supplementary Figure S5. The subgroup analysis based on the time-weighted average HbA1c

A.



B.

SUPPLEMENTARY DATA



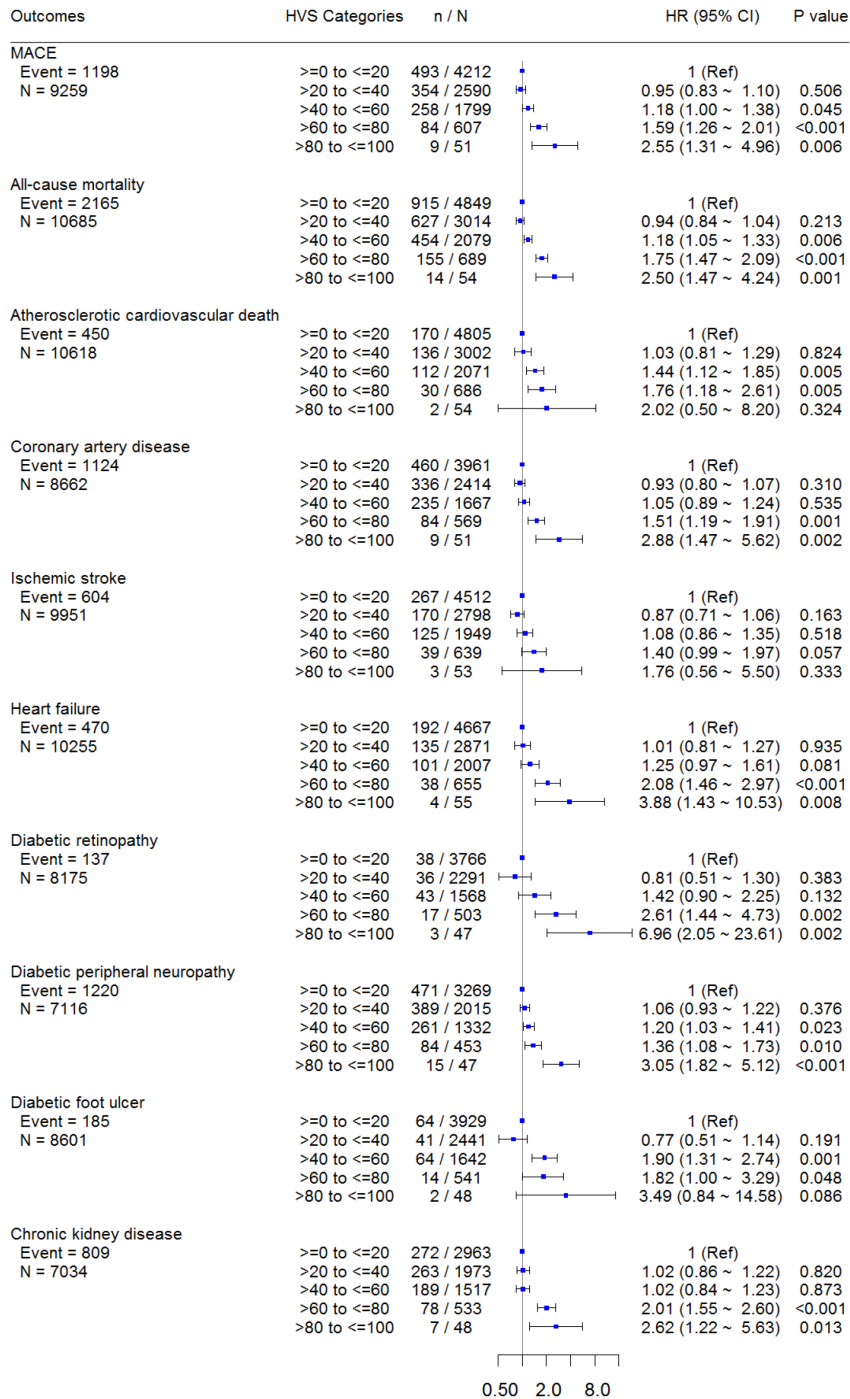
A. the subgroup of the time-weighted average HbA1c ≤7% (53 mmol/mol); B. the subgroup of the time-weighted average HbA1c >7% (53 mmol/mol)

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

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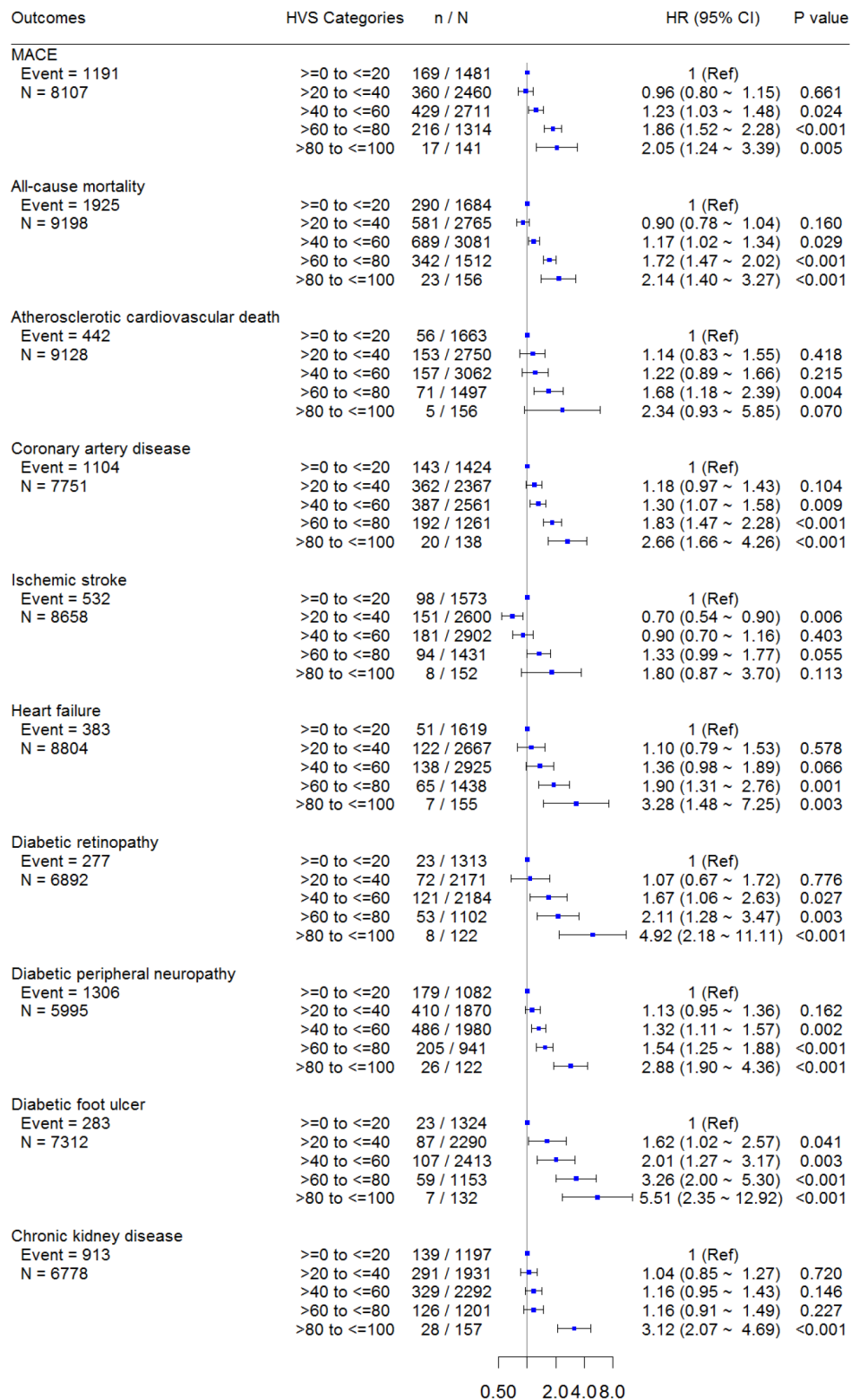
Supplementary Figure S6. The subgroup analysis based on the treatment of diabetes at baseline

A.



B.

SUPPLEMENTARY DATA

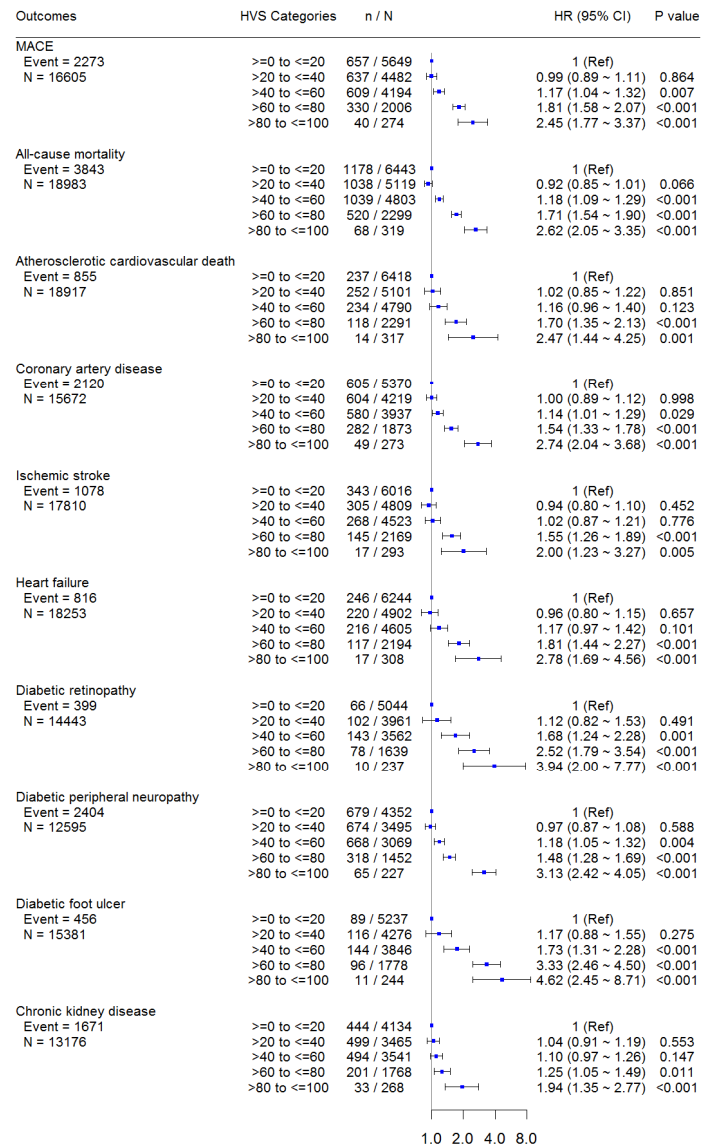


A. the subgroup of patients receiving lifestyle intervention only at baseline; B. the subgroup of patients receiving anti-diabetic medication or insulin at baseline

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

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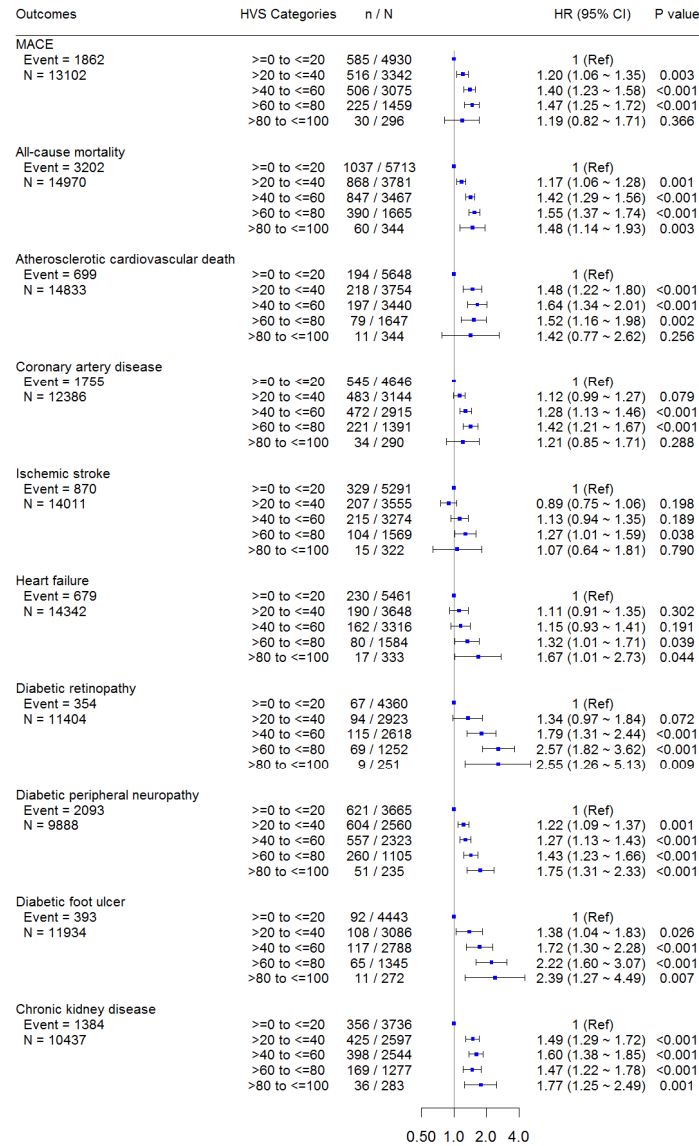
Supplementary Figure S7. The sensitivity analysis using the binned HbA1c variability score (b-HVS)



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

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

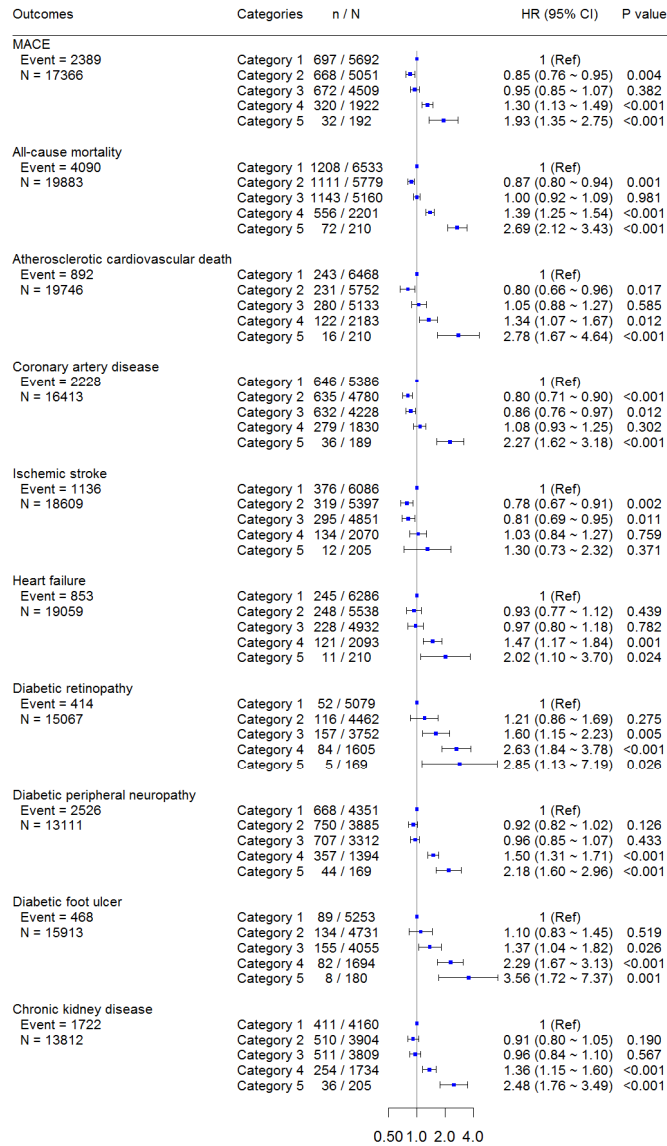


Abbreviations: CI: confidence interval; HR: hazard ratio; HVS: HbA1c variability score.



SUPPLEMENTARY DATA

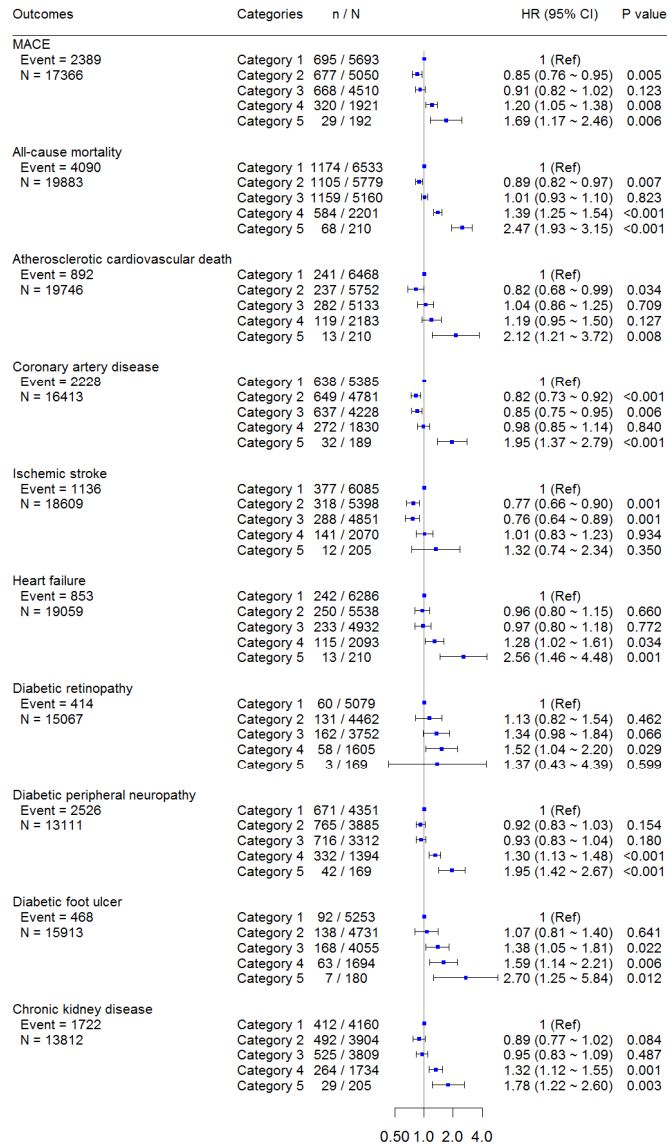
**Supplementary Figure S9. The sensitivity analysis using the standard deviation (SD) of the HbA1c levels in accordance with the HVS category**



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

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



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