Associations between usual glycated haemoglobin A1c and Cardiovascular Disease in Patients with Type 2 Diabetes Mellitus: A 10-year Diabetes cohort study

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ABSTRACT

Aims:

The long-term effect of glycated haemoglobin A1c(HbA1c) level on cardiovascular disease(CVD) risks among patients with type 2 diabetes remains controversial. The aim of this study was to investigate their associations.

Materials and methods:

This retrospective cohort study conducted in Hong Kong selected patients aged 45-84 years old with type 2 diabetes mellitus and without CVD in primary care clinics within 2008-2010. The usual HbA1c measurement was calculated using a mixed effects model to minimize regression dilution bias. The association between usual HbA1c and CVD risk was assessed by Cox regression with adjustment of baseline covariates. Subgroup analyses by patient characteristics were also conducted.

Results:

After a median follow-up period of 8.4years (1.4 million person-years), 174,028 patients with 34,074 CVD events were observed. Curvilinear association was found between the usual HbA1c and total CVD, stroke, heart failure and CVD mortality risk. No significant difference was found among patients with usual HbA1c<7% (53 mmol/mol). A positive linear association was found between usual HbA1c and the risks of outcomes when the HbA1c was 7% (53 mmol/mol) or above. The adjusted hazard ratios (HRs) for CVD risk per 1% increment in usual HbA1c>7%(53mmol/mol) was 21% (HR: 1.21; 95%C.I. (Confidence Interval): 1.18-1.23). Similar pattern was identified in patient's subgroups analysis, but the effect of usual HbA1c in younger patients were more prominent than the others.

Conclusions:

Increment in usual HbA1c level >7.0% (53mmol/mol) was associated with elevated CVD risk, but no difference was found in population with usual HbA1c<7.0% (53mmol/mol) irrespective of the patients' characteristics. For the CVD prevention, a strict adherence of HbA1c <7% (53 mmol/mol) should apply to patients with younger age.

Keywords:

Diabetes; Haemoglobin A1c; Cardiovascular Disease; Mortality

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease, affecting estimated approximately 425 million people worldwide [1]. DM is a significant cause of cardiovascular disease (CVD), with a relative two- to four-fold increased risk of cardiovascular morbidity and mortality compared to patients without DM [2]. Effective DM care is essential to reduce the risks of CVD event development, beginning with a valid and reliable measure to monitor glycemic control such as glycated haemoglobin A1c (HbA1c) [3, 4]. HbA1c is a well-recognized measure to reflects the average blood glucose level for the past two to three months. Existing guidelines tend to suggest a specific, patient-centred target HbA1c rather than a single generic target one [3], only limited studies supported this recommendation.

There have been four major trials investigating blood glucose control on the risks of CVD and mortality that produced contradictory findings [5-8]. The post-hoc analyses from UK Prospective Diabetes Study (UKPDS) found that intensive glucose lowering resulted in better CVD risk control [5], but no improvements in macrovascular disease after 10 years of intensive blood glucose control [9]. Conversely, the other three studies including Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) failed to showed that intensive glucose control show a reduction in macrovascular disease [6-8]. A number of observational studies also examined HbA1c control on CVD events, suggesting conflicting results[10-15]. The heterogenous shapes (U-shaped or J-shaped, or a positive curvilinear shape) from different studies demonstrating the association of HbA1c level and CVD risks left questions for the definition of optimal HbA1c control. Moreover, most of these observational studies did not incorporate regression dilution bias correction, which might further compromise the validity of their results.

The aim of this study is to investigate the effect of usual HbA1c level on CVD risks. The effect of age and other patient characteristics on usual HbA1c levels and CVD risks will also be explored.

MATERIALS AND METHODS

Study Design

This retrospective cohort study retrieved patient records from the clinical management system (CMS) electronic database from the Hong Kong Hospital Authority (HA), a Hong Kong Special Administrative Region government-managed institution. HA manages 73 primary care clinics, 47 specialist outpatient clinics, and 41 public hospitals in Hong Kong. In fact, the HA provides medical services and treatments for 90% of the Hong Kong population with chronic diseases [16]. The International Classification of Primary Care-2 (ICPC-2) coding system is used to record diagnostic data and the code T90 equates to a diagnosis of type-2 DM. Our study population included all patients aged 45 to 84 years with a T90 diagnostic code, a recorded HbA1c measurement and no previous history of CVD including heart failure, stroke, coronary heart disease such as myocardial infarction and angina pectoris, defined in **Supplemental Table S1**, at baseline who attended appointment with general practitioner in the general outpatient clinics in the HA between 1st January 2008 to 31st December 2010. The validity and coding accuracy were well-established as the CMS data had been previously adopted by various high-quality large population-level epidemiological studies [17, 18]. Clinical information and demographic characteristics of patients were recorded by clinic doctors and healthcare professionals who were trained and routinely used the CMS. Records included patients' diagnoses, prescriptions, laboratory tests and results, emergency department visits, hospitalizations, and specialist and primary care outpatient clinic visits. The baseline was set

the first date of HbA1c record between 2008 and 2010, and then each patient was follow-up until the incident date of outcome events, death, or the last follow-up visit up to 31 December 2017, whichever came first.

Outcomes Measures

The primary outcome was CVD events. The secondary outcomes included individual subtype of CVD events, which were heart failure, stroke, CHD events, and CVD mortality and all-cause mortality. Disease outcomes were identified by the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM), or the diagnosis codes of ICPC-2 [19]. Mortality reports were provided by the Hong Kong Government Death Registry, which is a population-based government official registry with all registered death records of all Hong Kong citizens . As defined by the International Classification of Diseases, Tenth Edition codes of I20-I25, I50, and I60-I69, all CVD-related mortality referred to the death with previous history of CVD or with CVD as the main cause of death; which were known to contain high coding accuracy in diagnoses of myocardial infarction and stroke with positive predictive values of 85.4% (95% confidence interval (CI) 78.8% to 90.6%) and 91.1% (83.2% to 96.1%), respectively. [18] **Supplemental Table S1** summarized all the diagnosis codes of ICPC-2 and ICD-9-CM for each individual event.

Ethics approval

Institutional Review Boards (IRB) of the Hong Kong Hospital Authority has reviewed and approved the ethical examination in this study.

Usual HbA1c Measurement

The usual HbA1c measurement was estimated from a mixed effect model, which differentiated individuals in order to minimize regression bias. By using the mixed effects model, this allowed for the adjustment the within-individual variability to differentiate between individuals, thus reducing regression dilution bias in the estimated association with the time-to-event outcome. Longitudinal trajectories were modelled by including a slope term as both a fixed and random effect. Bayesian Markov chain Monte Carlo was used to fit the mixed effects model. The usual HbA1c levels were estimated by the posterior mean of the random intercept, represented by the mean of HbA1c level corrected with regression dilution bias. In this study, all HbA1c records within 2 years before baseline were used to calculate the usual HbA1c. The average number of HbA1c records was 2.4 (SD: 1.0). The Bayesian framework using Markov Chain Monte Carlo with JAGS Version 4.3.0 and the R2jags package in R was used to estimate the usual HbA1c for each patient[20, 21]. The detailed statistical method could refer to the literature [22, 23].

Baseline characteristics

The baseline covariates consisted of age, gender, HbA1c, body mass index (BMI), diastolic blood pressure (DBP), systolic blood pressure (SBP), smoking status, low-density lipoprotein-cholesterol (LDL-C), the Charlson's comorbidity index[24], the use of anti-hypertensive drugs (e.g. angiotensin converting enzyme inhibitor or angiotensin receptor blocker (ACEI/ARB), β-blocker, calcium channel blocker (CCB), diuretics and others (hydralazine, methyldopa, and prazosin)), estimated glomerular filtration rate (eGFR) [25], oral anti-diabetic drugs (metformin, sulphonylurea and others), insulin, and lipid-lowering agents. All laboratory tests were taken place under the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia in accredited laboratories.

Data Analysis

All missing values for each baseline characteristic were imputed 5 times by multiple imputation using the chained equation method, with adjustment among all baseline covariates and outcomes. Same data analysis techniques were applied in each of the five imputed datasets and results were pooled based on Rubin's rule. [26]

The study population was divided into quintiles according to their usual HbA1c (<6.7% [49.2 mmol/mol], 6.7-7.2% [49.2-54.9 mmol/mol], 7.3-7.7% [55.0-60.7 mmol/mol], 7.8-8.4% [60.8-68.0 mmol/mol] and >8.4% [68.09 mmol/mol]). Some descriptive statistics were shown for integration of all baseline covariates in each subgroup. The cumulative incidence and incidence rate for CVD and mortality were shown with the estimated confidence interval (CI) of the incidence rate under Poisson distribution. Kaplan-Meier curves by groups were plotted. The association between usual HbA1c groups and the risks of CVD was demonstrated using multivariable Cox proportional hazards regression with adjustment of patient's baseline characteristic and usual HbA1c. Proportional hazards assumptions were assessed using plots of the scaled Schoenfeld residuals against time for the covariates. The models satisfied the proportional hazards assumption. The floating absolute risk was used to estimate the 95% C.I. of the hazard ratios without choosing the reference group to show the standard error. [27] Restricted cubic splines with three knots in Cox models were used for usual HbA1c, which was treated as a continuous variable in order to verify the shape of the association.[28] Three sensitivity analyses were performed to strengthen the robustness of the results and lower the potential bias due to multiple imputation, reverse causality, and number of HbA1c measurements. Firstly, a complete case analysis was performed. Secondly, all patients with less

than 1-year follow-up period were excluded. Thirdly, patients with 4 or more HbA1c measurements on or before baseline were included.

Subgroup analyses were conducted to further investigate the effect of usual HbA1c on CVD events with different characteristics based on gender (male, female), age (45-54, 55-64, 65-74, 75-84 years), smoking status (non-smoker, smoker), duration of DM (<5, ≥5 years), BMI (<25; ≥25kg/m^2), SBP (<130, ≥130mmHg), LDL-C (<2.6, ≥2.6mmol/L), eGFR (<90, ≥90ml/min/1.73m^2), Charlson's Index (<4, ≥4), the number of prescribed anti-hypertensive drugs (0, 1, ≥2).

All significance tests were two-tailed and those with a *p*-value less than 0.05 were regarded as statistically significant. The statistical analysis was conducted in Stata Version 13.0.

RESULTS

This retrospective cohort study included 249,145 patents with Type-2 DM between 2008 and 2010. After excluding patients with one or less HbA1c record within 2 years before baseline (29,404), CVD on or before baseline (45,402) or without follow-up after baseline (311), a total of 174,028 patients included in the analysis. **Supplemental Table S2** shows that almost all baseline characteristics had over 90% in data completion rate except for LDL-C (86.7%), BMI (80.1%) and smoking status (76.8%). **Table 1** summarizes all patients' characteristics in each usual HbA1c subgroup at baseline after multiple imputations. The average age was 64.1 years (SD: 10.0) among all subjects, with males accounted for 46.0% in total. The overall usual HbA1c was 7.5% (SD: 0.9). Kaplan-Meier curves by groups were plotted in the **Supplemental Figure 2**. **Table 2** illustrates the cumulative incidence and incidence rate of CVD, CVD mortality, and their composite events in each usual HbA1c subgroup. After a median follow-

up period of 8.4 years (1.4 million person-years), the overall number of incidents of CVD and CVD mortality were 34,072 and 3,719, respectively. Generally, there was an increasing trend of the usual HbA1c against the cumulative incidence and incidence rate of all outcomes, from the group with the lowest usual HbA1c (<6.65% [49.18 mmol/mol]) to the group with the highest usual HbA1c (≥8.38% [68.09 mmol/mol]), involving CVD events ranging from 25.8 to 29.8, CVD mortality ranging from 2.5 to 3.2 and their composite events ranging from 26.3 to 30.3 per 1000 person-years. **Figure 1** demonstrates the adjusted hazard ratio for the risks of CVD, CHD, stroke, heart failure, CVD mortality and their composite events using multivariable Cox regression adjusted with patient's characteristics. The curvilinear associations between the usual HbA1c and the risks of CVD, stroke, heart failure and CVD mortality were obtained. No significant difference was found below usual HbA1c of 7% (53 mmol/mol) and positive linear associations between usual HbA1c and risks of outcomes above usual HbA1c of 7% (53 mmol/mol) was suggested. Meanwhile, direct linear association with no usual HbA1c threshold between usual HbA1c and the risks of CHD was observed. **Supplemental Figure S1** displays the results of the restricted cubic spline, showing the similar shape of the association between each individual CVD, CHD, stroke and heart failure event, CVD mortality and their composite events. **Figure 2** shows the adjusted hazard ratios for the risk of all individual CVD, CHD, stroke and heart failure events, CVD mortality and their composite events for every 1% increment in usual HbA1c among all subjects with usual HbA1c ≥7% (53 mmol/mol). 1% greater in usual HbA1c was associated with 21% (HR: 1.21 [95% CI 1.18-1.23]) and 37% (HR: 1.37 [95% CI 1.29-1.46]) higher risk of CVD and CVD mortality, respectively. The three sensitivity analyses, including the complete case analysis, the analyses involving all subjects with 12 months or longer follow-up period and that with 4 or more HbA1c measurements on or before baseline, indicated similar results in **Supplemental Figure S2**.

The results from subgroup analyses by stratifying patient's characteristics were showed in **Figure 3.** Age, LDL-C level, Charlson's index and the number of anti-diabetic drugs used were interacted with the effect of usual HbA1c on the risks of CVD. This implied that the effect of usual HbA1c in patients with younger age, higher LDL-C, or less comorbidities used were more prominent than the others. Other characteristics did not appear to affect the association between usual HbA1c and CVD risks.

DISCUSSION

This large cohort study investigated the association between usual HbA1c and the risks of CVD, CHD, stroke, heart failure, CVD mortality and all composite outcomes among patients with diabetes in Hong Kong. A curvilinear association was identified between usual HbA1c and the risks of all CVD events and mortality except for CHD which showed a positive log-linear association. The usual HbA1c effect on patients with younger age was stronger compared to those with older age. This further suggested that low usual HbA1c level did not necessarily provide additional protective effect over CVD risks. Therefore, patient-centred targets might optimize clinical benefits for individual patients.

Compared with the four major study trials, our findings were different from that of the UKPDS [5]. This might be due to differences in the study populations and outcome measures. Moreover, the UKPDS, which started recruit patients in 1977, is a historically much older cohort with little use medications such as statins might also explain the differences. Our study comprised of a larger cohort who were not newly diagnosed with DM and thus had a relatively longer DM history and had a larger number of outcome events compared with the UKPDS. UKPDS, a population-based prospective cohort, identified a linear risk association between

HbA1c and the incidence of CVD, CHD, heart failure, stroke, and CVD mortality. Similar to other RCTs, our study design included the participation of elderly patients, and the underrepresentation of this subgroup in the UKPDS might further contribute to our differences in results.

The other three landmark trials (ACCORD, ADVANCE, and VADT) found that intensive glucose control in type 2 DM patients resulted in no significant difference in the incidence of macrovascular disease. In other words, the findings suggested that an approach that focused solely on aggressive reduction of HbA1c would not be effective in lowering macrovascular disease incidence [6-8]. For the rest of the cardiovascular event parameters, a much lower HbA1c level did not necessarily correspond to a decreased CVD risk. One of the possible reasons could be the resultant severe hypoglycemia experienced by patients with low HbA1c level, which had been suggested by other large-scale international studies such as ADVANCE and ACCORD [6, 7]. Acute hypoglycemia could provoke physiological changes to haematological parameters such as haemorrheological changes, white blood cell activation, vasoconstriction and the release of inflammatory mediators that adversely affect the cardiovascular system.[29]

In terms of the CHD outcome, ADVANCE and VADT showed no benefit to CHD risk with intensive control of glucose. However, our results concurred with that of the ACCORD trial which demonstrated the lower the HbA1c level, the lower the risks of CHD. This was also consistent with a systematic review which suggested intensive HbA1c control significantly reduced CHD incidence in particular [11]. Another study illustrated similar findings that HbA1c 4.6% or above was associated with an increased risk of CHD in patients without

diabetes although the underlying mechanisms were not clear. [30] Further studies should be conducted to understand the mechanisms between HbA1c and CHD.

In term of epidemiological studies, a previous large study using he Swedish National Diabetes Register obtained the U-shape in all-cause mortality, but supported the current findings that the positive curvilinear shape between HbA1c and CVD [2]. The discrepancy findings in all-cause mortality may be related to the reserve causality. Compared to Swedish study, the multiple measurements of HbA1c, and the sensitivity analysis by excluding patients with less than 1-year follow-up were conducted in the current study. While another observational study using the Diabetes & Aging cohort reported similar conclusion on all-cause mortality, this study obtained a positive linear relationship between HbA1c and CVD events among newly diagnosed patients [31]. A legacy effect or metabolic memory attributed to an intensive initial glucose control on CVD **[32, 33]** may explain the inconsistent results in CVD **[32, 33]**. **A**chieving lower HbA1c target in newly diagnosed patients with diabetes may have long-lasting benefits in CVD prevention. However, further investigations should be conducted to confirm the findings.

Our key findings indicated the effect of usual HbA1c was stronger among younger patients as compared with the older ones. This may suggest that older patients are subject to conditions such as physiological decline, chronic degenerative diseases and even the clustering of multiple diseases, all of which may mitigate the severity of the CVD risks. [34] It is possible that having more comorbidities, as reflected by Charlson's index, overshadows the effect of HbA1c. A local study also suggested that the reduction in absolute and relative mortality were less likely to be found in patients with diabetes aged 45 years or less in the past 20 years, calling for immediate action on improving diabetes care services for this particular population group [35].

Strengths and Limitations of this study

The major strength of this observational study is the inclusion of a large type 2 DM cohort with a long period of follow-up up to ten years. The evidence from this large-scale study with a long-time frame is robust enough to demonstrate the association between different usual HbA1c level and the CVD-related outcome events in different subgroups. Secondly, regression dilution bias was reduced by using appropriate statistical analysis methods. A comprehensive evaluation of the association between usual HbA1c level and the adverse clinical outcomes were concluded with the sensitivity analyses. Multiple imputations were also performed to impute missing data so as to reduce selection bias. Finally, a wide range of relevant baseline covariates, including patients' laboratory results with high coverage, disease attributes and treatment modalities, were considered in order to produce reliable results with the aid of HA's computerised administrative database.

There are also limitations in our study. First of all, the study design of a retrospective cohort study allowed us to conclude that there were significant associations between HbA1c level and outcomes but not the causation of outcome events. However, a low probability of reverse causation was observed as patients with CVD at baseline were excluded in this study. Moreover, the sensitivity analysis yielded similar results when we only included patients with a follow-up period more than one year. Secondly, potential confounding factors related to specific treatment modalities such as type of anti-hypertensive drugs, follow-up medications and the length of drug prescription, and lifestyles including physical activity level and dietary intake, were not assessed in our study. However, we considered patients' anthropometric and clinical parameters, such as BMI, SBP, lipid profile and eGFR, which potentially reflects the severity of their diseases and lifestyle habits. Lastly, the findings from this study might not be

applicable to other countries or settings with different ethnic or sociocultural differences. Even the association between different usual HbA1c level and their relative CVD risk was well-presented, this could possibly be due to the individual differences among our sampled subjects, compared to the general population and the type 2 DM populations from other Chinese regions. Temporal variations and alterations in non-assessed risk factors or interventions might induce heterogeneity in the association.

CONCLUSION

In this population-based cohort study of Chinese primary care patients with type 2 DM, a curvilinear association was demonstrated between usual HbA1c and the risks of CVD, stroke, heart failure, CVD mortality and all composite outcomes while a positive linear association was found between HbA1c and the risks of CHD. An increment in usual HbA1c level of above 7.0% was associated with an increased risk in CVD events and all-cause mortality. The associations between usual HbA1c level and mortality rate seemed stronger among younger patients and those with higher LDL-C level and less comorbidities. Additional monitoring and a patient-centred clinical approach to these groups of patients might be beneficial. Future studies are needed to investigate a therapeutic target for HbA1c level to provide better outcomes for patients with type 2 DM.

Author Contributions

E.Y.F.W., and C.L.K.L. contributed to the study design and acquisition of data, researched the data, contributed to the statistical analysis and interpretation of the results, and wrote the manuscript. E.Y.T.Y. and J. Y. C. contributed to the interpretation of the results and wrote the manuscript. All authors reviewed and edited the manuscript. E.Y.F.W. is the guarantor of this

work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of interest

I.C.K.W. received funding from Pfizer, Bayer and Novartis to evaluate real world evidence on pharmacological treatments of cardiovascular diseases but not related to current study. E.W.Y.C. received research grants from Bayer, Bristol-Myers Squibb, Janssen, a Division of Johnson and Johnson, Pfizer, and Takeda to evaluate real world evidence on pharmacological treatments of cardiovascular diseases but not related to current study. Other authors declare that they have no competing interests.

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Tables

Table 1. Baseline characteristics among subjects, stratified by usual HbA1c

	Usual HbA1c (%)					Overall (N=174,028)
	(<6.7% [49.2 mmol/mol] (N = 34,806)	6.7-7.2% [49.2-54.9 mmol/mol] (N = 34,806)	7.3-7.7% [55.0-60.7 mmol/mol] (N = 34,805)	7.8-8.4% [60.8-68.0 mmol/mol] (N = 34,806)	>8.4% [68.09 mmol/mol] (N = 34,805)	
Male	47.4%	43.9%	43.1%	44.7%	50.9%	46.0%
Age, years	65.4 (10.2)	65.1 (10.0)	64.6 (9.9)	63.7 (9.9)	61.7 (9.8)	64.1 (10.0)
Current smoker	8.8%	9.3%	10.1%	11.2%	14.9%	10.9%
Duration of diabetes	5.8 (6.0)	6.5 (6.3)	7.4 (6.8)	8.2 (7.4)	7.8 (7.4)	7.1 (6.7)
Usual HbA1c, %	6.2 (0.4)	6.9 (0.2)	7.4 (0.2)	8.0 (0.2)	8.8 (0.3)	7.5 (0.9)
SBP, mmHg	135.4 (17.6)	135.8 (17.2)	136.6 (17.4)	137.2 (17.6)	137.4 (18.6)	136.5 (17.7)
DBP, mmHg	74.1 (10.3)	74.5 (10.2)	74.8 (10.1)	75.7 (10.3)	76.8 (10.2)	75.2 (10.3)
BMI, kg/m^2	25.2 (4.5)	25.5 (4.7)	25.6 (4.3)	25.6 (4.5)	25.3 (4.1)	25.4 (4.1)
LDL-C, mmol/L	3.0 (0.9)	3.1 (0.9)	3.1 (0.9)	3.1 (0.9)	3.1 (1.0)	3.1 (0.9)
eGFR, $ml/min/1.73m^2$	98.4 (41.6)	99.3 (52.9)	99.9 (44.7)	101.0 (30.0)	105.3 (32.3)	100.8 (41.9)
Charlson Index	3.3 (1.4)	3.2 (1.4)	3.2 (1.4)	3.1 (1.4)	2.9 (1.4)	3.1 (1.4)
Use of oral anti-hypertensive drugs	74.1%	73.1%	72.1%	69.3%	61.1%	69.9%
Use of Metformin	47.8%	57.6%	70.3%	78.6%	82.3%	67.3%
Use of Sulphonylurea	36.9%	43.4%	55.3%	68.1%	74.2%	55.6%
Use of other oral DM drugs	0.8%	1.0%	1.7%	3.4%	9.3%	3.2%
Use of Insulin	0.7%	0.9%	1.5%	2.9%	8.5%	2.9%
Use of lipid-lowering agents	10.0%	11.1%	10.8%	10.5%	11.4%	10.8%

BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HbA1c = Haemoglobin A1c; LDL-C = Low-density Lipoprotein-Cholesterol;

Notes:
All parameters are expressed in either percentage or mean (SD).

Table 2. Number, incidence rate and hazard ratio of CVD, CHD, stroke, heart failure, CVD mortality and all cause mortality stratified by usual HbA1c

	Usual HbA1c (%)				
	(<6.7% [49.2 mmol/mol] (N = 34,806)	6.7-7.2% [49.2-54.9 mmol/mol] (N = 34,806)	7.3-7.7% [55.0-60.7 mmol/mol] (N = 34,805)	7.8-8.4% [60.8-68.0 mmol/mol] (N = 34,806)	>8.4% [68.09 mmol/mol] (N = 34,805)
CVD					
Cumulative cases with event	6,373	6,528	6,792	6,994	7,385
Crude Incidence rate (95% CI)†	25.8 (25.2, 26.5)	26.1 (25.4, 26.7)	26.8 (26.2, 27.5)	27.6 (26.9, 28.2)	29.8 (29.2, 30.5)
Hazard ratio (95% CI)‡	1.00 (0.97,1.03)	1.02 (0.99,1.04)	1.05 (1.02,1.07)	1.11 (1.08,1.13)	1.34 (1.30,1.37)
Coronary heart disease					
Cumulative cases with event	2,797	3,089	3,191	3,399	3,667
Crude Incidence rate (95% CI)†	10.8 (10.4, 11.2)	11.8 (11.4, 12.2)	12.0 (11.6, 12.4)	12.7 (12.3, 13.2)	14.1 (13.6, 14.5)
Hazard ratio (95% CI)‡	1.00 (0.96,1.04)	1.09 (1.05,1.13)	1.11 (1.07,1.14)	1.19 (1.15,1.23)	1.39 (1.35,1.44)
Stroke					
Cumulative cases with event	3,156	3,132	3,368	3,380	3,523
Crude Incidence rate (95% CI)†	12.2 (11.8, 12.7)	11.9 (11.5, 12.4)	12.7 (12.3, 13.1)	12.7 (12.3, 13.1)	13.5 (13.1, 14.0)
Hazard ratio (95% CI)‡	1.00 (0.96,1.04)	0.98 (0.95,1.02)	1.05 (1.02,1.09)	1.09 (1.05,1.12)	1.30 (1.26,1.35)
Heart failure					
Cumulative cases with event	1,760	1,759	1,773	2,026	2,346
Crude Incidence rate (95% CI)†	6.7 (6.4, 7.0)	6.6 (6.3, 6.9)	6.5 (6.2, 6.8)	7.4 (7.1, 7.8)	8.8 (8.5, 9.2)
Hazard ratio (95% CI)‡	1.00 (0.95,1.05)	0.99 (0.94,1.04)	0.99 (0.94,1.03)	1.17 (1.12,1.22)	1.63 (1.56,1.71)
CVD mortality					
Cumulative cases with event	674	700	706	759	880
Crude Incidence rate (95% CI)†	2.5 (2.3, 2.7)	2.6 (2.4, 2.8)	2.6 (2.4, 2.8)	2.7 (2.5, 2.9)	3.2 (3.0, 3.5)
Hazard ratio (95% CI)‡	1.00 (0.92,1.08)	1.03 (0.96,1.11)	1.02 (0.95,1.10)	1.13 (1.05,1.21)	1.55 (1.44,1.67)
All cause mortality					
Cumulative cases with event	5,415	5,272	5,400	5,675	6,322
Crude Incidence rate (95% CI)†	20.3 (19.7, 20.8)	19.3 (18.8, 19.9)	19.5 (19.0, 20.0)	20.4 (19.9, 20.9)	23.2 (22.7, 23.8)
Hazard ratio (95% CI)‡	1.00 (0.97,1.03)	1.00 (0.97,1.03)	1.02 (0.99,1.05)	1.09 (1.07,1.12)	1.39 (1.35,1.42)

† Incidence rate (cases/1000 person-years) with 95% CI based on Poisson distribution.

‡ Hazard ratio was adjusted by age, gender, smoking status, duration of diabetes, body mass index, systolic and diastolic blood pressure, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of metformin, sulphonylurea, other oral diabetic drugs, insulin, anti-hypertensive drugs, lipid-lowering agent, Charlson's index at baseline and usual HbA1c. CIs are displayed as floating absolute risks. HbA1c = Haemoglobin A1c; CVD = Cardiovascular disease; CHD = Coronary heart disease; CI = Confidence interval.

Figure legends

Figure 1. Title: Adjusted Hazard ratio for incidence of CVD, CHD, Stroke, Heart failure, CVD mortality and all-cause mortality with increment usual HbA1c by multivariable Cox regressions.

Figure 2. Title: Adjusted hazard ratios for the risk of CVD, coronary heart disease, stroke, heart failure, CVD mortality and all-cause mortality with each 1% increment usual HbA1c in patients with HbA1c of ≥ 7% using multivariable Cox regressions.

Figure 3. Title: Adjusted hazard ratios for the risk of CVD compared to patients with quintile 1 of HbA1c (<6.7%) by stratifying patient's characteristics at baseline using multivariable Cox regressions.