Age-specific Associations of HbA1c Variability with Cardiovascular Disease and Mortality in Type 2 Diabetes Mellitus Patients: A 10-year cohort study

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Abstract

Aims:
The detrimental effect of increased variability in glycated Haemoglobin(HbA1c) on cardiovascular disease(CVD) and mortality risk in patients with diabetes remains unclear. The aim of this study was to investigate their associations.,

Materials and Methods:
This prospective cohort study included 147,811 patients aged 45-84 years with type2 diabetes mellitus, without CVD and attained at least three HbA1c records before baseline within 2008-2010. HbA1c variability was obtained using a mixed effects model to reduce regression dilution bias. Age-specific associations(45-54;55-64;65-74;75-84years) between HbA1c variability and risk of CVD and mortality were assessed by Cox regression adjusted for patient characteristics and usual HbA1c.

Results:
After a median follow-up of 7.4 years(1.02 million person-years), an overall incidence of 40,785 events including CVD(27,793 incidence) and all-cause mortalities(23,175 incidence) were identified. Positive log-linear associations between HbA1c variability and CVD and mortality were identified in all age groups. The hazard ratios (HRs) for the composite of CVD and all-cause mortality revealed age was inversely associated with HbA1c variability, with a 28% higher risk per 1% increase in HbA1c variability in the 45-54 age group[all composite outcomes HR:1.28(1.21,1.35)], whereas only a 14% higher risk in the 75-84 age group[all composite outcomes HR:1.14(1.11,1.17)]. Subgroup analysis showed the risk in patients with usual HbA1c<7% was about eight times more than those with usual HbA1c≥8%.

Conclusions:
HbA1c variability was strongly related to CVD and mortality in patients with diabetes across all age groups. Whilst pursuing optimal HbA1c target, attention should be given to patients with high HbA1c variability especially those young ones with good HbA1c control.

Keywords:
Diabetes; Variability; Glycated Haemoglobin; Cardiovascular Disease; Mortality

Manuscript Text

Introduction

Diabetes mellitus (DM) is a growing pandemic that affects 415 million people worldwide, and the figure is estimated to reach 693 million by 2045[1]. The risk of CVD among patients with diabetes is about two to three fold higher than those without [2]. Cardiovascular disease is a leading cause of death, accounting for 33% of overall mortality [3]. The healthcare cost was increased by 360% after a major cardiovascular incidence [4]. Glycated Haemoglobin (HbA1c) is one of the recommended clinical parameters for regular monitoring of glycemic control for the primary prevention of CVD by several international guidelines on diabetes management [5,6]. Apart from the absolute reading of HbA1c, there is an emerging concern that HbA1c variability might be linked to CVD and mortality [7], but this relationship remains unclear.

A previous systematic review and meta-analysis based on seven studies suggested that there is an association between HbA1c variability and the risk of CVD and mortality among patients with type 2 DM [8]. Together with more recent studies, a total of 14 studies have examined these relationships [8-14], however only eight studies included CVD as the outcome measurement [8,10-13]. One study found no association between HbA1c variability and CVD [15]. Nevertheless, most of these studies were limited with either a small sample size, low number of incident outcomes, short follow-up period, or without adjustments for potential confounders such as duration of diabetes, comorbidities, and baseline medications [8]. In addition, almost all of the current available studies defined HbA1c variability using the values during follow-up, but analyzed it as a baseline exposure. This might lead to a possible immortal time bias so that the death of studied patients could not occur earlier because of the immortal time up until the studied patients satisfying the certain numbers of HbA1c measurements [16]. Only one post-hoc analysis

of the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR controlled Evaluation (ADVANCE) randomized controlled trial (RCT) based on 4,399 patients with a median follow-up of 3.0 years established the HbA1c variability based on the values by baseline [17]. However, the inclusion criteria of RCTs are usually strict so the results may not be applicable to larger, more heterogeneous population with diabetes. More importantly, the association from all available studies were conducted without correcting for regression dilution bias so that the HbA1c variability was evaluated on a person-by-person basis, and thus subject to measurement error [18]. Furthermore, as previous studies have identified that the effect of HbA1c levels may vary among younger and older patients with diabetes, it would also be valuable to evaluate the effect by different age subgroups [19-21].

The aim of this study is to investigate the age-specific associations between HbA1c variability and risk of CVD and mortality in patients with type 2 DM managed in primary care settings. We will also examine the patterns of variability among patients with different baseline characteristics. The findings could contribute to a better understanding of the role of HbA1c variability in CVD and mortality to inform clinicians on how to identify patients at higher risks at earlier stage of illness and guide the management of HbA1c variability.

Materials and Methods

Study Design

This is a population-based prospective cohort study using electronic health records managed by the Hong Kong Hospital Authority (HA). Patients aged 45-84 years, clinically diagnosed with type 2 DM, with no prior diagnosis of CVD at baseline, who had at least three HbA1c records, and who were managed in public primary care clinics under the HA from 1 January 2008 to 31 December 2010 were included in the cohort. In Hong Kong, the HA plays an

important role in the healthcare system as the sole regulatory institution for all 42 public-sector hospitals, 47 specialist outpatient clinics and 73 primary care clinics. Due to their large health subsidies, more than 90% of the local Hong Kong population with chronic illnesses receive their medical treatments through the HA [22]. Type 2 DM clinical diagnoses were made by HA clinic doctors and were identified using the International Classification of Primary Care-2 (ICPC-2) code of T90. All the confidential data of the patients, including their characteristics and event outcomes, are kept in the electronic health database of the HA's clinical management system. The validity and coding accuracy of the CMS database is well-established, and CMS data has been previously adopted in several high-quality population-based epidemiological studies [23-25]. In terms of data accuracy and consistency, training on how to record patients' demographics and clinical information including diagnoses, prescriptions, laboratory tests and results in emergency department, hospitalizations and specialist and primary care outpatient clinic visits using the CMS is routinely provided to all HA clinicians and other allied healthcare providers. The current study adopted the design similar to the post-hoc analysis of ADVANCE RCT that divided the follow-up into HbA1c assessment and outcome ascertainment periods in order to avoid using the post-baseline HbA1c values. Annual HbA1c test is recommended for patients with diabetes managed in Hong Kong primary care settings. In order to obtain at least three HbA1c values for increasing the precision of HbA1c variability, the HbA1c assessment period was set to be two years. The baseline was set after the first date of HbA1c record, and then each patient was continuously tracked until the incident date of outcome events, death, or the last follow-up visit up to 31 December 2017, whichever came first. The detail of study design is described in the **Supplementary Figure 1**.

Outcome Measures

The primary outcome was the incidence of the composite of CVD and all-cause mortality. The secondary outcomes were comprised of individual CVD, the subtypes of coronary heart disease, stroke, heart failure, all-cause mortality, CVD mortality, and non-CVD mortality. The outcome events were defined using the ICPC-2 or the International Classification of Diseases, Ninth Edition, Clinical Modification. The mortality reports were provided by the Hong Kong Government Death Registry, with the cases retrieved from their internal population data. The CVD-related mortality was classified as the death with a history of CVD or the main cause of death record by the International Classification of Diseases, Tenth Edition codes of I20-I25, I50, and I60-I69. These codes had revealed a high coding accuracy in previous studies in the 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 [24]. All the definitions for individual events were outlined in **Supplementary Table 1**.

HbA1c Measurements

HbA1c was measured by high-performance liquid chromatography (Biorad Variant II Turbo) or equivalent. All blood samples were analyzed at the authorized laboratory with the same protocol under Hospital Authority management. All laboratory assays were performed in accredited laboratories by the College of American Pathologists, the Hong Kong Accreditation Service, or the National Association of Testing Authorities, Australia.

Usual HbA1c and HbA1c variability Measurements

To minimize regression dilution bias, usual HbA1c and HbA1c variability measures were obtained using a mixed effects model. This allowed the within-individual variability to differentiate between individuals. 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 and HbA1c variability were estimated by the posterior mean of the random intercept and the residual standard deviation, respectively. The method described by Barrett et al was used to the calculate usual HbA1c and HbA1c variability measures [26]. In general, usual HbA1c and HbA1c variability were calculated based on the mean and SD with the regression dilution correction. The average total number of HbA1c measurements was 3.2 (Standard deviation: 0.8). The analysis was implemented using JAGS Version 3.4.0 and the R2jags package in R [27,28].

Baseline characteristics

Baseline covariates included gender, age, smoking status, duration of diabetes, BMI, systolic and diastolic blood pressure, low-density lipoprotein-cholesterol (LDL-C), estimated glomerular filtration rate (eGFR), the Charlson's comorbidity index [29,30], the use of anti-hypertensive drug, oral anti-diabetic drugs including metformin, sulphonylurea and other oral DM drugs, insulin, and lipid-lowering agents. The eGFR was computed in accordance with the creatinine level from blood testing along with the abbreviated Modification of Diet in Renal Disease Study formula recalibrated for Chinese (eGFR in ml/min/1.73 m^2 = 186 × [(serum creatinine in μmol/L) × 0.011] -1.154 × $(age)^{-0.203}$ × (0.742 if female) × 1.233, where 1.233 is the adjusted coefficient for local population [31].

Ethical approval

Institutional Review Boards of the Hong Kong Hospital Authority reviewed and approved this study.

Data Analysis

Multiple imputation was used to impute missing data for all baseline characteristics apart from HbA1c. The chained equation method was used to impute each missing value five times, adjusted for all baseline covariates and outcomes. The same analysis method was adopted for each of the five imputed datasets, and the results were pooled using Rubin's rule [32].

All patients were allocated into one of ten groups defined by 0.25% of HbA1c variability increments between 0% and 2.5% (e.g. 0-0.24%, 0.25-0.5%, …, 2.25-2.5%), 2.5-2.99% and ≥3%. After multiple imputation, descriptive statistics were displayed for integration of the baseline characteristics for each group. The cumulative incidence and incidence rate of CVD, mortality, and their composite events were reported and the confidence interval (CI) of the incidence rate was estimated using the Poisson distribution. Age-specific associations (45-54, 55-64, 65-74 and 75-84 years) between HbA1c variability and the risk of an event were estimated by multivariable Cox proportional hazards regressions adjusted for baseline characteristics and usual HbA1c. An additional term was fitted to allow the HR within each age group to be assessed as the geometric mean of the HRs in the first and second half of that decade [33]. Thus, the hazard ratios comparing event risk between different HbA1c variability groups were not assumed to be similar for different age decades. The 95% CI of the hazard ratios were estimated using the floating absolute risk, without the requirement of selecting a reference group for displaying the standard error [34]. Details of the above methods had previously been described in the literature [33,34], and widely adopted in several large epidemiological studies [35-37]. To confirm the shape of the association, restricted cubic splines with three knots in Cox models were used for HbA1c variability, treated as a continuous variable [38]. To enhance the robustness of the results, other variability measurements such as coefficient of variation and variability independent of mean rather than SD were used. Three sensitivity analyses were conducted. Firstly, a complete case analysis was performed. Secondly, patients were excluded if they

attended less than 1-year follow-up. Thirdly, the analyses were implemented for patients with ≥ 5 HbA1c measurements during the assessment period.

To further explore the effect of HbA1c variability on the outcomes for patients with different characteristics, subgroup analyses were performed which were stratified by gender (male; female), age at risk (45-54, 55-64, 65-74, 75-84 years), smoking status (non-smoker, smoker), duration of diabetes (<5; ≥5years), BMI (< 25; ≥ 25kg/m^2), usual HbA1c (<7%, 7-7.9%, 8-8.9%, ≥9%), LDL-C (< 2.6, ≥ 2.6mmol/L), eGFR (< 90, ≥ 90ml/min/1.73m^2), and Charlson's Index (< 4, ≥ 4).

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

Results

After applying the inclusion criteria on the cohort subjects, 147,811 patients with T2DM were included for analysis. Data completion rates for all baseline characteristics were over 90%, except for BMI (86.9%), as illustrated in **Supplementary Table 2. Table 1** summarizes the patients' baseline characteristics for different subgroups of HbA1c variability after multiple imputations. Overall, the mean age was 64.2 years (SD: 10.0) with males accounting for 46.0%. Usual HbA1c mean and variability were 7.5% (SD: 0.9) and 0.8% (SD: 0.7) respectively.

A median follow-up of 7.4 years (1.02 million person-years), the overall number of event incidence was 40,785, including both CVD (27,793 incidence) and all-cause mortalities (23,175 incidence) as shown in **Figure 2**. In **Table 2,** the cumulative cases and incidence rate of CVD, all-cause mortality and their composite events stratified by HbA1c variability group

were presented. A growing trend was observed with incidence rates of all outcomes followed by increases in the HbA1c variability subgroups. Comparing the lowest HbA1c variability group (0-0.24%) with the highest group (≥3.0%), the incidence rate showed increasing trend from 23.5 to 33.6 in CVD incidence, from 17.9 to 33.2 in mortality, from 35.1 to 52.4 incidence in all events per 1,000 person-years respectively. **Supplementary Figure 2** demonstrates the positive and log-linear association between HbA1c variability and all event outcomes after the adjustment of the patients' baseline characteristics. The result of the restricted cubic spline HbA1c variability association in the Cox models as indicated in **Supplementary Figure 3** also suggested the log-linear association. While in the age-specific association as demonstrated in **Figure 1,** positive and log-linear associations between the HbA1c variability and the risk of leading to CVD, all-cause mortality and all the composite event outcomes were also found in all age groups. Similar patterns were obtained using other variability measurements such as coefficient of variation and variability independent of mean rather than SD.

Figure 2 demonstrates the association of continual HbA1c variability and the risk of developing adverse outcome events. When the HbA1c variability increased by 1%, the risk of CVD, all-cause mortality and all composite events also increased by 15% (HR:1.15 [95% CI 1.12-1.18]), 32% (HR: 1.32 [95% CI 1.29-1.36]) and 19% (HR: 1.19 [95% CI 1.17-1.22]) respectively. Among all the CVD event outcomes, the HR for heart failure was the highest (HR: 1.29 [95% CI 1.23-1.35]), followed by stroke (HR: 1.18 [95% CI 1.13-1.22]) and CHD (HR: 1.06 [95% CI 1.02-1.10]), indicating that the risk of developing heart failure were most predominant among patients with cardiovascular disease and diabetes. Similarly, comparing CVD and non-CVD related mortality, cardiovascular mortality (HR: 1.38 [95% CI 1.33-1.44]) was higher than that of non-CVD related (HR: 1.26 [95% CI 1.21-1.31]), implying cardiovascular diseases contributed to higher mortality risks. Three sensitivity analyses

including (1) complete case analysis, (2) patients with at least 12-month follow-up period and (3) patients with at least five HbA1c measurements on or before baseline in **Supplementary Figure 4** showed similar results.

In **Figure 3,** the forest plots demonstrated that an increase in HbA1c variability was associated with different degrees of risk for developing adverse event outcomes among subgroups with different baseline characteristics. The most pronounced risk difference was demonstrated by patients with different usual HbA1c at baseline. The HRs for the risk of CVD and all-cause mortality are higher among patients with usual HbA1c <7.9% [all composite outcomes HR for 7-7.9%: 1.35 (1.27, 1.42)], with the highest risk among those whose usual HbA1c were <7% [all composite outcomes HR: 1.83 (1.66, 2.03)]. Comparing the risk of patients with usual HbA1c <7% and those with usual HbA1c≥8%, the risk of the former group was about 8 times more than the latter group, with all composite outcomes HR for 8-8.9% and ≥9% usual HbA1c groups: 1.10 (1.06, 1.14) and 1.12 (1.08, 1.16) respectively. The HRs for the composite of CVD and all-cause mortality show that age is inversely associated with the usual HbA1c variability, with 28% higher risk per 1% increase in HbA1c variability in the 45 to 54- year-old group [all composite outcomes HR: 1.28 (1.21, 1.35)], whereas only 14% higher risk in the 75 to 84-year-old group [all composite outcomes HR: 1.14 (1.11, 1.17)]. This indicates a double of risk in the 45 to 54-year-old group than that of the 70 to 79-year-old group. Moreover, the HR is higher among patients with longer duration of diabetes (≥5 years). Comparable effect is observed when stratified by gender, smoking status, BMI, baseline systolic blood pressure, LDL-C, eGFR and the indication of morbidity (Charlson's index <4 and ≥4).

Discussion

This large study is the first to investigate the age-specific associations between HbA1c variability and risk CVD and mortality among Chinese patients with diabetes. Our study demonstrated a positive log-linear association between HbA1c variability and risk of CVD and all-cause mortality, irrespective of age. The impact of HbA1c variability effect on young patients with lower usual HbA1c and longer duration of diabetes was strengthen compared to the others. Our results remained significant after the multiple adjustments such as usual HbA1c, immortal, informative and regression dilution bias, recommending that clinicians should be cautious for HbA1c variability other than the optimal HbA1c target, in particular for patients with younger age, lower usual HbA1c or longer diabetes duration.

Our analyses found that the strength of HbA1c variability effect on CVD and mortality decreased with age or HbA1c. A recent observational study using the Clinical Practice Research Datalink (CPRD) showed that the magnitude of HbA1c variability effect on mortality in patients aged 40-64 years old was higher compared to those aged 65-89 years old but the impact in patients with ≤6.58% was smaller than that in those with >7.91%, although both trend were not significant [39]. However, they used categorical variables instead of continuous variables that was used in our study, direct comparison may be inappropriate. In their study, a small proportion of patients aged 40-59 years old (n=13,508), with HbA1c of ≤6.58 (n=14,703) were included; and they had relatively short follow-up period (mean: 4.1 years) [39]. In contrast to our study, we included more young patients and had a longer follow-up period, which led to sufficient power to detect the differences. It is possible that older patients were frail and may have experienced weight loss, sarcopenia and high burden form other comorbidities, and thus it could unknowingly overshadow the HbA1c variability effect. Younger patients with fewer vascular risk factors may have therefore been more susceptible to HbA1c variability. Similar explanations for HbA1c, it is well-recognized that increase in

HbA1c is associated with higher risk of CVD and mortality, and thus may mask the HbA1c variability effect. Moreover, patients with high HbA1c were more likely to have higher HbA1c variability shown in Table 1, which echoed with previous study [40]. These patients may tolerate more continual variability than other. As a result, patients with low HbA1c may be more sensitive to HbA1c variability, and will therefore have a higher risk of CVD and mortality than those with high HbA1c. Apart from age and HbA1c, our findings also showed the magnitude of HbA1c variability effect increased with diabetes duration. Patient with longer diabetes duration had lower HbA1c variability shown in Table 1. Again, one interpretation is that patients with longer diabetes duration are more vulnerable to HbA1c variability, and that with short diabetes duration, the contribution of variability is less pronounced. Further detailed analysis of biological mechanisms for these findings is warranted to confirm the explanations.

Our findings showed a direct log-linear association between HbA1c variability and risk of CVD and all-cause mortality which was consistent with most previous studies [8-14]. A cross-sectional study conducted on 8,290 Italian patients with diabetes concluded that there was no association between HbA1c variability and CVD risk [15]. One potential explanation is attributable to the different study designs. A longitudinal study design in our study with large number of patients and long follow-up period could provide more reliable results on the effect of HbA1c variability compared to this cross-sectional study. It is also worth mentioning that the effect of HbA1c variability on CVD [HR:1.27(1.15-1.40)] and mortality [HR:1.34(1.18-1.53)] in previous meta-analysis were higher than that observed in our study [8]. The reason may be related to immortal, informative and regression dilution bias on previous studies which did not adjust for potential confounders such as mean HbA1c [8]. Moreover, their analysis included patients managed in primary secondary and tertiary care settings, whilst all of our patients were managed in primary care. Possible reasons could be our population were

healthier compared to those in other studies and direct comparison might not be appropriate. Further studies should be conducted to confirm our results.

The association of HbA1c variability and CVD risk and all-cause mortality could be explained by several possible underlying mechanisms. From a pathophysiological perspective, intermittent hyperglycaemia is more effective in producing reactive oxygen than chronic hyperglycaemia, eventually impairing endothelial function and causing changes in epigenetics, activating the release of cytokines [41,42]. The acceleration in atherosclerosis development is related to inflammation, oxidative stress and endothelial dysfunction. This will lead to an increased risk in the development of CVD and mortality [43,44]. Intermittent hyperglycaemia induces higher levels of apoptosis and lower levels of the insulin secretory capacity in pancreatic beta cells than chronic hyperglycaemia [45,46], thus the reduction in pancreatic beta cell function may worsen glycaemic control. This could eventually progress to CVD and death. Meanwhile, hypoglycaemia could possibly also be one of the risk factors predisposing to CVD and all-cause mortality due to inflammation, blood coagulation abnormality, sympathoadrenal response and endothelial dysfunction [2,47]. Studies have shown that glucose variability can be associated with an increased risk of hypoglycaemia [48,49]. However, these studies only reflected the effect of short-term glycaemic variability. A recent observational study showed the association between long-term HbA1c variability and mortality were attenuated but not explained by hypoglycaemia [39]. As the association between long-term HbA1c variability and various adverse outcomes is not well-established, more research is needed to investigate the underlying mechanism explaining the relationship between long term glucose variability and CVD risk and all-cause mortality.

Strengths and Limitations of this study

The strength of this study involved a large population of patients with diabetes who were Chinese and representatives of primary care patients receiving treatment for diabetes in Hong Kong. In addition, the clinical characteristics captured by the HA's computerised administrative database allowed access to relevant information such as anthropometric and laboratory data. Several advanced statistical methods were used to reduce potential bias including immortal, informative and regression dilution bias.

There are also several limitations. Firstly, the prospective cohort study design is less highly ranked in terms of the hierarchy of evidence. Secondly, drug adherence, quality of life improvement, infection prevention and lifestyle interventions such as reduction in excessive drinking, regular exercise and diet modification which contribute to reducing the risks of CVD and mortality were not measured in the present analysis. However, disease characteristics such as duration of diabetes, and key clinical parameters such as body mass index, blood pressure, and lipid, to a certain extent, reflect the intensity of disease severity and lifestyle modification have been considered. Thirdly, the large numbers of observations may make p-value irrelevant and the long-term effects of variability in HbA1c on the risks of CVD event and all-cause mortality are uncertain among Chinese patients with diabetes.

Conclusions

This population-based cohort study demonstrated a positive log-linear association between variability in HbA1c and incidence of CVD and all-cause mortality among Chinese primary care patients with type 2 DM. Compared to the older group, the detrimental effects of HbA1c variability on the risks of CVD and all-cause mortality in the younger group were higher. The HbA1c variability may provide additional valuable information as a potential predictor for the

development of CVD and all-cause mortality among patients with diabetes. Clinicians should monitor for HbA1c fluctuations in addition to the absolute value.

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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., W.Y.C., F.T.Y.N., S.M.C.C., I.C.K.W., E.W.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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