

ASCVD risk stratification modifies the effect of HbA1c on cardiovascular events among patients with type 2 diabetes mellitus with basic to moderate risk

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ABSTRACT

Objective To investigate the association between hemoglobin A1c (HbA1c) 7.0%–8.0% and cardiovascular disease (CVD) risk among Chinese patients with type 2 diabetes mellitus (T2DM) with different baseline 10-year atherosclerotic CVD (ASCVD) risk stratification.

Research design and methods A prospective population-based cohort of 10 060 adults aged 40–70 years in Chongming District of Shanghai was established in 2011. These participants were followed up for 3.25 years and CVD information was recorded. We investigated this association between HbA1c categories and incident CVD stratified by the 10-year ASCVD risk using multiple Cox regression analysis among 1880 patients with T2DM without CVD history. CVD events were defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke.

Results The corresponding incidence of CVD per 1000 person-years for the HbA1c ≤6.5%, 6.6%–6.9%, 7.0%–8.0% and >8.0% groups were 12.5, 21.8, 22.9 and 28.9, respectively. The HbA1c >8.0% group was significantly associated with a higher CVD risk in patients with T2DM. The HbA1c 7.0%–8.0% group was significantly associated with a higher CVD risk in patients with T2DM with moderate baseline ASCVD risk (HR 2.48; 95% CI 1.15 to 5.32).

Conclusion HbA1c of 7.0%–8.0% may result in a significantly higher CVD risk among patients with T2DM with moderate baseline ASCVD risk, which support the use of HbA1c combined with baseline ASCVD risk assessment to determine future glucose-lowering treatment decisions among patients with T2DM with basic to moderate risk.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality for individuals with diabetes and the greatest contributor to direct and indirect costs of diabetes.¹ As a marker to identify the average plasma glucose concentration during preceding 10–12 weeks, hemoglobin A1c (HbA1c) was used to monitor the control

Significance of this study

What is already known about this subject?

► Hemoglobin A1c (HbA1c) >8.0% group was significantly associated with a higher cardiovascular disease (CVD) risk in patients with type 2 diabetes mellitus (T2DM).

What are the new findings?

► HbA1c of 7.0%–8.0% may result in a significantly higher CVD risk among patients with T2DM with moderate baseline atherosclerotic CVD (ASCVD) risk.

How might these results change the focus of research or clinical practice?

► Using HbA1c combined with baseline ASCVD risk assessment to determine future glucose-lowering treatment decisions among patients with T2DM with basic to moderate risk.

of blood glucose in patients with diabetes.² Despite abundant observational studies and clinical trials having demonstrated an association between HbA1c and cardiovascular disease (CVD) events, there is conflicting evidence regarding appropriate HbA1c targets for reducing CVD events in patients with type 2 diabetes mellitus (T2DM).

Since the American College of Physicians published a guidance statement on HbA1c targets for glycemic control with pharmacological therapy for non-pregnant adults with patients with T2DM in March 2018 which recommended that clinicians should aim to achieve an HbA1c level between 7.0% and 8.0% in most patients with T2DM, significant controversy has arose around the applicability of the guideline to patients with T2DM with HbA1c 7.0%–8.0%.^{3–5} Experts from American Diabetes Association believed the recommendation is at odds with those of

other professional organization and suggested that a reasonable HbA1c goal for many non-pregnant adults is $<7\%$.

ASCVD risk score is a comprehensive index for evaluation of the risk of future CVD events. Cardiovascular risk stratification is widely used for evaluating the risk of hypertension-related CVD events^{6–8} and blood lipid management.⁹ However, there was no study to investigate the effect of ASCVD risk stratification on management of hyperglycemia in patients with T2DM, whether in observational studies or randomized clinical trials.

In our previous study, we had found that patients with T2DM and an increased baseline 10-year ASCVD risk may increase the CVD events in the future.¹⁰ In the present population-based prospective cohort study, we explored the incidence of CVD caused by various HbA1c categories among individuals with T2DM and first investigated this association stratified by the 10-year ASCVD risk.

RESEARCH DESIGN AND METHODS

Study population

The participants in this study were from the Chengqiao Town, Chongming District of Shanghai, China. Of 45 876 residents aged 40–70 years in the whole Chengqiao town, we randomly sampled 10 060 subjects to conduct our study using a stratified cluster sampling method. All eligible individuals within each of the selected community/street were sampled. Informed consent was obtained from all participants.

At baseline in 2011, a total of 10 060 subjects were recruited, among which 9930 had full information. The questionnaire and inquiry method used in this study were adopted from the Risk Evaluation of cAncers in Chinese diabeTic Individuals: A lONgitudinal (REACTION) study.¹¹ We used 75 g oral glucose tolerance test (OGTT) to assess 2-hour glucose for those without known T2DM and used 100 g steamed bread that contained approximately similar carbohydrates for those with self-reported T2DM.¹² Of the 9930 participants, 2484 had T2DM. At the end of 3.25 years of follow-up, 581 subjects with T2DM did not attend the study, and the rest 1903 patients with T2DM in the cohort were followed up. After excluding 23 participants with previous CVD history, 1880 patients with T2DM were analyzed in this study (figure 1). Among the 1880 patients with T2DM, 61% of them are newly diagnosed.

Study end points

Cardiovascular events were documented as having cardiovascular death, coronary heart disease and cerebrovascular disease. Coronary heart disease was further defined as non-fatal myocardial infarction and coronary revascularization. Cerebrovascular disease includes cerebral hemorrhage and cerebral infarction from any cause. Information on cardiovascular deaths was obtained from the official death certificates of Chongming district.

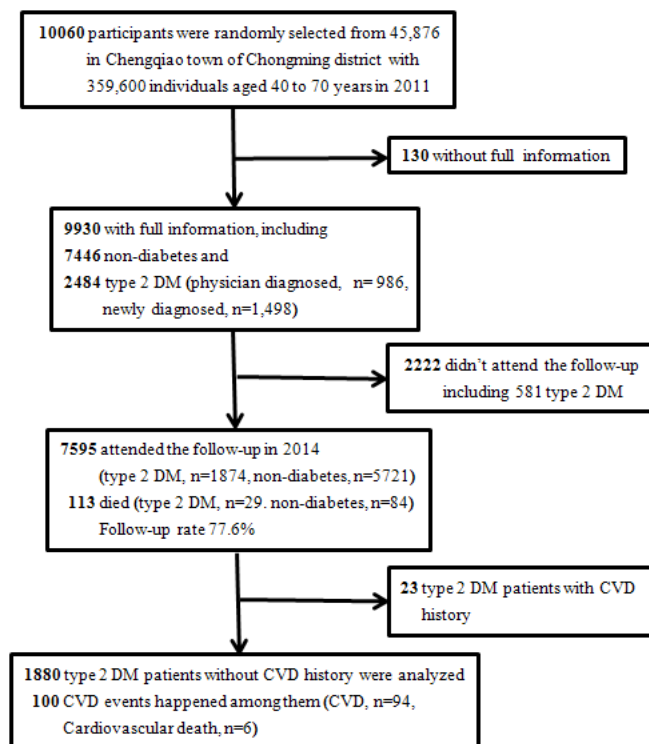


Figure 1 Participant flow diagram. CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus.

Blood glucose and HbA1c measurement

Plasma glucose was measured during a 75 g OGTT, and T2DM was defined by a fasting plasma glucose level ≥ 7.0 mmol/L and/or a 2-hour postchallenge glucose level ≥ 11.1 mmol/L, a previous physician diagnosis of T2DM or use of antidiabetic medication at baseline. Plasma glucose and HbA1c were measured using the same methods as described before.¹³

Other variables of interest

Triglycerides (TG), total serum cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol were measured on an automatic analyzer (Hitachi 7080; Japan). Fasting insulin was determined by RIA (Linco Research, USA). Anthropometric measurements were conducted by 20 well-trained nurses or postgraduates. Medical history, smoking and drinking information were gathered by a questionnaire.

We adopted the equations developed by Yang *et al*¹⁴ to calculate the ASCVD risk score, which evolved from The Framingham Heart Study,¹⁵ but is more suitable for Chinese people. For the group with ASCVD risk score $\geq 10\%$, the mean and range of baseline 10-year ASCVD risk was 13.4% (11.7%–17.1%) in this study; we defined the group as moderate ASCVD risk group. The baseline 10-year ASCVD risk score $<10\%$ group was basic ASCVD risk group.

Statistical analysis

For database management and statistical analysis, we used SAS V.9.2 software. Data were presented as means \pm SD,

median (IQR) or number (%). One-way analysis of variance was used to compare the differences between groups at baseline. The log-rank test was used to compare the cumulative incidence of CVD between groups, with the Kaplan-Meier survival function to show the time to events. Unadjusted and adjusted HRs for cardiovascular events according to different HbA1c levels were estimated using Cox proportional hazards models. P values <0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics

The cohort information was detailed in [figure 1](#). The baseline characteristics of 1880 patients with T2DM are shown in [table 1](#) according to different HbA1c levels. Participants with HbA1c of 7.0%–8.0% group were found to be more likely to have greater age and TG levels but lower HDL-C levels than that in the HbA1c≤6.5% group. Moreover, we compared the baseline characteristics in participants with T2DM who attended the follow-up study with those who did not and found no significant difference in glucose levels, blood lipid profile, systolic blood pressure and diastolic blood pressure between the two groups.

These patients with diabetes in our cohort had two special characteristics: 1) all patients were from a population-based cohort, 61% of these are newly diagnosed patients with diabetes and 2) the baseline 10-year ASCVD risk ranged from basic to moderate, there was no patient at higher ASCVD risk (baseline 10-year ASCVD risk >40%).

HbA1c category and CVD

During the follow-up, 100 patients with T2DM (5.3%) experienced a first CVD event, and the corresponding incidence of CVD per 1000 person-years for the HbA1c≤6.5%, 6.6%–7%, 7.0%–8.0% and >8% groups were 12.5, 21.8, 22.9 and 28.9, respectively. Kaplan-Meier survival curve for CVD events according to different HbA1c levels is shown in online supplementary figure 1.

[Table 2](#) displays the HRs and 95% CIs for cardiovascular events by different HbA1c categories. Taken HbA1c≤6.5% as the reference, the HR for cardiovascular events was not significantly different in HbA1c 6.6%–6.9% group. A baseline HbA1c 7.0%–8.0% had a 1.84 times higher risk of developing CVD in the crude model. However, HbA1c 7.0%–8.0% did not significantly elevate the CVD risk when compared with the reference group after adjusting for age, sex and other factors, with HR of 1.72% and 95% CI 0.98 to 3.04. HbA1c>8.0% was significantly associated with development of CVD both in the crude model (HR 2.31; 95% CI 1.38 to 3.83) and in the adjusted model (HR 2.34; 95% CI 1.12 to 4.90).

HbA1c categories combined with baseline 10-year ASCVD risk and CVD

[Table 3](#) showed the HRs and 95% CIs for cardiovascular events according to different HbA1c categories combined

with baseline 10-year ASCVD risk. The participants were divided into four groups according to different HbA1c levels (≤6.5%, 6.6%–6.9%, 7.0%–8.0% or >8.0%) and further divided into eight groups according to both HbA1c levels and the baseline 10-year ASCVD risk score.

Taken HbA1c below 6.5% and basic baseline ASCVD risk group as the reference, HbA1c>8% was significantly associated with a higher CVD risk in the general patients with T2DM, and the HR was 2.11 (95% CI 1.11 to 4.02) for basic ASCVD risk group, and 3.34 (95% CI 1.60 to 6.97) for moderate ASCVD risk group, respectively. However, the HbA1c 7.0%–8.0% group was significantly associated with a higher CVD risk in patients with moderate ASCVD risk group (HR 2.48; 95% CI 1.15 to 5.32; p=0.02), but not in those with basic ASCVD risk group. The HbA1c 6.6%–6.9% group was not significantly associated with a higher CVD risk no matter in basic or moderate baseline ASCVD risk group.

The combined effects of various HbA1c categories and ASCVD risk stratification on the incidence of CVD are shown in [figure 2](#). Rates per 1000 person-years were calculated in these eight groups.

DISCUSSION

Our study investigated the CVD risk caused by HbA1c 7.0%–8.0% in a Chinese population-based cohort and found to the best of our knowledge for the first time that HbA1c 7.0%–8.0% may result in a significantly higher CVD risk in Chinese patients with T2DM with moderate baseline ASCVD risk.

There is conflicting evidence regarding appropriate HbA1c targets for reducing CVD events in patients with T2DM. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial,¹⁶ ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation) trial¹⁷ and Veterans Affairs Diabetes Trial (VADT)¹⁸ did not observe significant difference in cardiovascular outcomes between intensive and standard treatment groups. However, in two separate UK Prospective Diabetes Study (UKPDS) 33 and UKPDS 34 trials,^{19 20} there were more benefits attained from intensive treatment compared with conventional therapy. Evidence from the above different trials has not consistently shown beneficial effects of HbA1c targets between 7.0% and 8.0% on reducing macrovascular events and death. Baseline ASCVD risk might be an important confounder and an explanation for conflicting results in patients with T2DM.

The accurate assessment of individual risk can be of great value to guiding and facilitating the prevention of ASCVD.²¹ As early as in 1976, the Framingham Heart Study identified several risk factors and developed the first coronary heart disease risk equations.²² Since then, several tools for CVD risk evaluation have been published and have guided public health and clinical practice in different populations.^{15 23 24} However, these equations were all derived from Western samples, which limited their applicability to other populations. Yang *et al*¹⁴

Table 1 Baseline characteristics of subjects with different HbA1c levels

Characteristics	All	HbA1c ≤6.5%	HbA1c 6.6%–6.9%	HbA1c 7.0%–8.0%	HbA1c >8.0%	P value
N	1880	961	271	346	302	
Age (years)	59.1±6.9	58.7±7.0	58.8±6.6	60.3±6.5	59.0±6.9	0.004
Male, n (%)	739 (39.3)	378 (39.3)	101 (37.3)	134 (38.7)	126 (41.7)	0.74
BMI (kg/m ²)	25.5±3.5	25.4±3.5	26.1±4.2	25.7±3.1	25.2±3.3	0.014
Waist-to-hip ratio	0.90±0.06	0.90±0.06	0.91±0.08	0.91±0.06	0.91±0.06	<0.0001
SBP (mm Hg)	137.9±18.1	138.0±18.5	137.2±15.5	138.6±18.5	137.5±18.3	0.76
DBP (mm Hg)	82.0±9.7	82.4±9.9	81.5±7.9	81.8±9.5	81.6±10.7	0.39
HbA1c	7.0±1.5	5.96±0.4	6.7±0.1	7.4±0.3	9.8±1.6	<0.0001
FPG (mmol/L)	8.1±2.5	6.9±1.0	7.6±1.0	8.5±1.4	12±3.5	<0.0001
2hPG (mmol/L)	13.7±4.5	11.7±3.0	13.1±2.8	14.8±3.4	19.3±5.3	<0.0001
HDL-C (mmol/L)	1.2±0.3	1.25±0.34	1.17±0.30	1.16±0.27	1.16±0.27	<0.0001
LDL-C (mmol/L)	2.7±0.8	2.7±0.8	2.8±0.9	2.7±0.8	2.8±0.8	0.42
TC (mmol/L)	4.8±1.1	4.94±1.1	4.8±1.1	4.8±1.0	4.9±1.1	0.89
TG (mmol/L)	1.65 (1.15–2.46)	1.58 (1.11–2.39)	1.68 (1.13–2.48)	1.73 (1.28–2.57)	1.67 (1.13–2.52)	0.04
Insulin	7.87 (5.30–11.10)	7.70 (5.20–11.10)	8.09 (5.38–11.30)	8.13 (5.52–11.50)	6.95 (4.80–10.50)	0.19
Hypertension, n (%)	1252 (66.6)	631 (65.9)	185 (68.3)	240 (69.4)	195 (64.8)	0.68
Antihypertension therapy, n (%)	413 (22.0)	211 (22.0)	72 (26.6)	83 (24.0)	47 (15.6)	0.009
Smoking, n (%)	342 (18.2)	163 (17.0)	41 (15.1)	64 (18.5)	74 (24.5)	0.01
Drinking, n (%)	425 (22.6)	204 (21.2)	64 (23.6)	84 (24.3)	73 (24.2)	0.54
ASCVD score ≥10%, n (%)	527 (28.0)	259 (27.0)	70 (25.8)	109 (31.5)	89 (29.5)	0.31
Newly diagnosed DM, n (%)	1151 (61.2)	770 (80.1)	155 (57.2)	140 (40.5)	86 (28.5)	<0.001
Diabetes duration of previous DM (years)	6.0 (2.0–9.0)	4.0 (2.0–6.7)	4.0 (2.0–7.0)	5.0 (2.5–8.0)	7.0 (4.0–11.0)	<0.001

Data are means±SD or number (%) or median (IQR).

ASCVD, atherosclerotic CVD; BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; 2hPG, 2-hour postchallenge glucose; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total serum cholesterol; TG, triglycerides.

Table 2 Adjusted HRs and 95% CIs for cardiovascular events according to HbA1c categories in Chinese patients with T2DM without cardiovascular event history

HbA1c categories	N/total	Cases/1000 P-Ys	Crude HR (95% CI)	Adjusted HR (95% CI)	
				Model 1	Model 2
HbA1c ≤6.5%	35/961	12.5	1	1	1
HbA1c 6.6%–6.9%	17/271	21.8	1.74 (0.98 to 3.11)	1.76 (0.99 to 3.15)	1.77 (0.98 to 3.19)
HbA1c 7.0%–8.0%	23/346	22.9	1.84* (1.09 to 3.11)	1.69 (1.00 to 2.87)	1.72 (0.98 to 3.04)
HbA1c >8.0%	25/302	28.9	2.31** (1.38 to 3.86)	2.29** (1.37 to 3.83)	2.34* (1.12 to 4.90)

Model 1 adjusted for age and sex.

Model 2 further adjusted for age, sex, WHR, LDL-C, HDL-C, TG, TC, FPG, 2hPG, hypertension history and current smoking.

*P<0.05, **p<0.01.

FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; 2hPG, 2-hour postchallenge glucose; LDL-C, low-density lipoprotein cholesterol; P-Ys, person-years; TC, total serum cholesterol; T2DM, type 2 diabetes mellitus; TG, triglycerides; WHR, waist-to-hip ratio.

conducted the China-PAR project to develop and validate the Chinese ASCVD risk equations in multiple contemporary Chinese cohorts. The risk prediction equations provided a valuable tool to quantify risk and to guide individualized primary care among Chinese populations.

The current population-based prospective cohort enabled us to explore the incidence of CVD among individuals with different HbA1c categories among patients with T2DM. As expected, we found that HbA1c>8.0% groups were significantly associated with a higher CVD risk in the general patients with T2DM (HR 2.34, 95% CI 1.12 to 4.90). However, after adjusting for age, sex and other factors, the HbA1c 7.0%–8.0% group was not significantly associated with a higher CVD risk in the general patients with T2DM. Our results were in line with the work by Palta *et al.*²⁵ They uncovered an important findings that an HbA1c>8.0% was associated with increased risk of all-cause and cause-specific mortality in older adults with diabetes from the National Health and Nutrition Examination Surveys.

Our study further extend on existing literature by combining ASCVD score evaluation for individualized glycemic targets and we put our emphasis on the question of whether the combination of HbA1c and ASCVD risk score is predictive of incident CVD events. In our study, the HbA1c 7.0%–8.0% group was significantly associated with a

higher CVD risk in patients with moderate baseline ASCVD risk (2.48, 95% CI 1.15 to 5.32), but not in those with basic baseline ASCVD risk. We provided the first data on the occurrence of CVD among Chinese adults combined with HbA1c 7.0%–8.0% and an estimated 10-year ASCVD risk, which supports the use of baseline ASCVD risk assessment to determine future treatment decisions among patients with T2DM with basic to moderate risk.

Limitations included the follow-up duration of about 3.25 years with CVD information recorded; 3.25 years may be relatively short and future studies with continuous follow-up of these participants are warranted to evaluate long-term health implications. Because therapies varied within groups, the impact on the outcomes of changes in HbA1c throughout follow-up is not being reported at this time. Because all patients with diabetes were from a Chinese population-based cohort and 61% of them were newly diagnosed patients with T2DM, there was no patient at higher ASCVD risk (baseline 10-year ASCVD risk >40%). Future studies are needed to discuss the association among patients with T2DM with different characteristics.

CONCLUSION

This study confirms that HbA1c 7.0%–8.0% combined with moderate baseline ASCVD risk may result in higher CVD

Table 3 Adjusted HRs and 95% CIs for cardiovascular events according to HbA1c categories and ASCVD risk score

HbA1c	ASCVD score	N/total	Cases/1000	HR (95% CI)	P value
			P-Ys		
HbA1c ≤6.5%	Basic ASCVD risk	24/702	11.7	1	/
	Moderate ASCVD risk	11/259	14.7	1.26 (0.62 to 2.57)	0.53
HbA1c 6.6%–6.9%	Basic ASCVD risk	13/201	22.5	1.93 (0.98 to 3.78)	0.06
	Moderate ASCVD risk	4/70	19.7	1.69 (0.59 to 4.86)	0.33
HbA1c 7.0%–8.0%	Basic ASCVD risk	14/237	20.2	1.74 (0.90 to 3.36)	0.10
	Moderate ASCVD risk	9/109	28.9	2.48* (1.15 to 5.32)	0.02
HbA1c >8.0%	Basic ASCVD risk	15/213	24.6	2.11* (1.11 to 4.02)	0.02
	Moderate ASCVD risk	10/89	38.9	3.34** (1.60 to 6.97)	0.00

*P<0.05, **p<0.01.

ASCVD, atherosclerotic CVD; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; P-Ys, person-years.

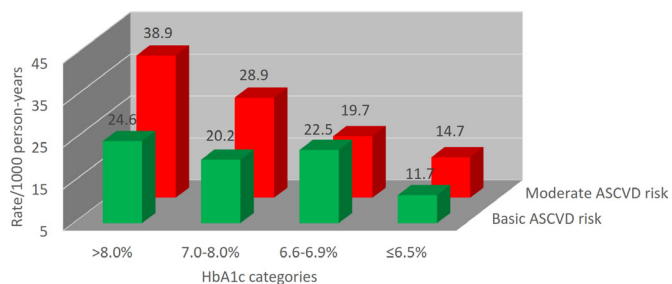


Figure 2 The effect of various HbA1c categories and ASCVD risk stratification combined on the prevalence of CVD among Chinese patients with T2DM. Rates per 1000 person-years were calculated in these eight groups. ASCVD, atherosclerotic CVD; CVD, cardiovascular disease; HbA1c, hemoglobin A1c; T2DM, type 2 diabetes mellitus.

risk among Chinese patients with T2DM. It is reasonable for patients with T2DM with HbA1c 7.0%–8.0% to have individualized treatment. In order to prevent CVD morbidity and mortality, more active intervention including pharmacological treatment should be strengthened among subjects with HbA1c 7.0%–8.0% and moderate baseline ASCVD risk. As to subjects with HbA1c 7.0%–8.0% and basic baseline ASCVD risk, a regular monitoring of blood pressure, glycemia and blood lipid in case of possible concurrent disorders are recommended.

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Competing interests None declared.

Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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