JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

General glycosylated hemoglobin goals potentially increase myocardial infarction severity in diabetes patients with comorbidities: Insights from a nationwide multicenter study

Qianzi Che[1], Yan Zhang[2], Jianan Wang[3], Zheng Wan[4], Xianghua Fu[5], Jiyan Chen[6], Hongbing Yan[7], Yundai Chen[8], Junbo Ge[9], Dafang Chen[1]*, Yong Huo[2]*

[1]Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing, China, [2]Department of Cardiology, Peking University First Hospital, Beijing, China, [3]Department of Cardiology, The Second Affiliated Hospital, Zhejiang University, Hangzhou, China, [4]Department of Cardiology, Tianjin Medical University General Hospital, Tianjin, China, [5]Department of Cardiology, Second Hospital of Hebei Medical University, Shijiazhuang, China, [6]Department of Cardiology, Guangdong General Hospital, Guangzhou, China, [7]Department of Cardiology, Chinese Academy of Medical Sciences & Peking Union Medical College Fuwai Hospital, Beijing, China, [8]Department of Cardiology, Chinese PLA General Hospital, Beijing, China, and [9]Department of Cardiology, Zhongshan Hospital Fudan University, Shanghai, China

Keywords
Diabetes mellitus, Glycosylated hemoglobin, ST-segment elevation myocardial infarction

***Correspondence**
Dafang Chen
Tel.: +86-10-8280-2644
Fax: +86-10-8280-2644
E-mail address:
dafangchen@bjmu.edu.cn

Yong Huo
Tel.: +86-10-8357-2283
Fax: +86-10-6613-7748
E-mail address:
huoyong@263.net

J Diabetes Investig 2020; 11: 1498–1506

doi: 10.1111/jdi.13287

Clinical Trial Registry
China STEMI Care Project
NCT03821012

ABSTRACT

Aims/Introduction: We aimed to investigate the relationship between glycemic status and coronary artery disease (CAD) extent and severity in ST-elevation myocardial infarction (STEMI) patients, and further examine whether diabetes patients could benefit from glycosylated hemoglobin (HbA1c) below the recommended level.

Materials and Methods: Consecutive STEMI patients admitted in 2015–2017 across 244 hospitals were included in the China STEMI Care Project-2. We carried out a cross-sectional study comprising 8,370 participants with a record of HbA1c testing after admission. CAD extent and severity were assessed by admission heart rate, Killip classification and the number of stenosed vessels based on the coronary angiogram.

Results: Diabetes patients showed a greater risk for higher Killip class, admission tachycardia (admission heart rate ≥100 b.p.m.) and multivessel CAD (presence of left main and/or triple vessel disease). Likewise, HbA1c level was significantly associated with CAD extent and severity. While dividing diabetes patients according to general HbA1c targets (HbA1c ≤6.5, 6.5–7.0 and ≥7.0%), diabetes patients with HbA1c ≤6.5% showed a 1.30-fold higher risk for multivessel CAD (adjusted odds ratio 1.30, 95% confidence interval 1.05–1.62). In stratified analysis, the association was even stronger in patients with hypertension (adjusted odds ratio 1.41, 95% confidence interval 1.08–1.86) or hyperlipidemia (adjusted odds ratio 1.57, 95% confidence interval 1.17–2.12).

Conclusions: HbA1c level is independently correlated with CAD extent and severity in STEMI patients. HbA1c below generally recommended levels might still increase the risk of CAD progression, especially for diabetes patients with hypertension or hyperlipidemia.

INTRODUCTION

Coronary artery disease (CAD) is the major contributor to death and disability among diabetes mellitus patients[1]. As the most serious type of acute coronary syndromes, ST-elevation myocardial infarction (STEMI) is an acute life-threatening illness that requires emergency care. Therefore, it is crucial to assess the extent and severity of STEMI with optimal physiological parameters. Admission heart rate (AHR) and Killip classification are fundamental indexes reflecting cardiac function and general condition. Both of them are important predictors of mortality in STEMI[2,3]. Coronary angiogram has long been the gold standard for evaluation of CAD, while the number of

Received 18 December 2019; revised 24 April 2020; accepted 29 April 2020

stenosed vessels based on angiographic evaluation is an early indicator to estimate the progression of CAD[4,5].

In addition to the well-established risk factor for CAD, diabetes mellitus is also associated with worse overall long-term prognosis in CAD patients. Compared with non-diabetes patients, diabetes patients with CAD have higher 10-year mortality[6] and increased morbidity, including greater burden of atherosclerosis, left ventricular dysfunction and angina[7]. Measurement of HbA1c has become a central pillar of diabetes mellitus diagnosis and management[8]. In several studies[9–11], but not all[12], HbA1c has a prognostic value to predict the severity and outcome of CAD.

Unfortunately, the association between HbA1c level and CAD can become even more complicated with the increasing prevalence of multimorbidity, which in many cases is also a risk factor for CAD. In the AMS Registry[13], diabetes mellitus and other comorbidities were shown to greatly influence clinical presentation and the outcome of patients admitted with acute coronary syndromes. In the Steno-2 Study[14,15], multifactorial risk factor control in diabetes mellitus patients effectively mitigated long-term risk of death and cardiovascular events. Thus, an intensified multiple risk factor intervention on CAD risk in patients with diabetes mellitus appears reasonable.

Long-term follow up in early trials has reported inconsistent results regarding the impact of tight glycemic control on CAD[16,17]. Given these findings from general diabetes population surveys, the study of targeted glycemic control in CAD patients with diabetes mellitus and comorbidities is warranted.

In the present study, we therefore investigated the relationship between HbA1c level and the extent and severity of STEMI, using AHR, Killip class and number of stenosed vessels, regarding comorbidity in a nationwide study population. Furthermore, we aimed to determine whether an HbA1c below general limits could potentially halt the progression of CAD in diabetes patients.

METHODS

Study site and population

The China STEMI Care Project-2 is a nationwide, multicenter and prospective study of patients hospitalized with a final diagnosis of STEMI, consecutively discharged from 244 percutaneous coronary intervention (PCI) hospitals in 14 provinces, municipalities and autonomous regions in China between 2015 and 2017. Hospitals are selected to establish a regional STEMI care network. Each hospital contributed to the study with at least 30 consecutive patients. Patients who met with the third acute myocardial infarction (MI) definition in 2012, and the Chinese STEMI diagnosis and treatment guideline, and within 1 month of symptom onset were enrolled, regardless of whether they were receiving reperfusion[18,19]. All patients underwent routine clinical assessment and treatment without any experimental intervention. The current analysis only considered patients from 242 hospitals who had a record of HbA1c testing after admission. A total of 12,429 patients were excluded due to the lack of information on HbA1c. After the exclusions, 8,370 participants were included in the cross-sectional study. For the analysis of the association of diabetes and HbA1c with multivessel CAD (MVD), we further excluded individuals who did not undergo a coronary angiogram (n = 2,332). Registry information of the project can be found in clinicaltrials.gov (No. NCT03821012)[20].

We carried out our studies in compliance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Peking University First Hospital[20].

Data collection procedures

Data of all treatment processes were entered into a self-built electronic database by qualified clinical research coordinators in each hospital[20]. For each case, the investigators collected demographic information, medical history, features of the presenting condition, electrocardiogram and biomarker findings, treatments before and during hospitalization, and follow-up management. All individual participants included in the study provided informed consent.

Definition of diabetes mellitus

HbA1c (%) was measured with an immunoturbidimetric International Federation of Clinical Chemistry and Laboratory Medicine-aligned method (Abbot Architect Analyzer, Abbott, Lake County, IL, USA). Diabetes mellitus was defined according to one of the following criteria: (i) self-reported diabetes mellitus that was previously diagnosed by physicians or the use of any antidiabetes mellitus therapy (oral medications or insulin-requiring) before hospitalization; (ii) diabetes mellitus listed in the medical records as the secondary discharge diagnosis; or (iii) HbA1c concentration ≥6.5% (≥48 mmol/mol).

Definition of Killip classification, tachycardia and multi-vessel CAD

Killip classification was determined by the attending physician on admission. Specifically, patients in Killip class I had no evidence of heart failure; class II patients had mild heart failure with rales involving one-third or less of the posterior lung fields and systolic blood pressure of ≥90 mmHg; class III patients had pulmonary edema with rales involving more than one-third of the posterior lung fields and systolic blood pressure of ≥90 mmHg; and patients in class IV were in cardiogenic shock with any rales and systolic blood pressure <90 mmHg[21]. Tachycardia was defined as an AHR ≥100 b.p.m.

The identification of MVD was based on the findings from a coronary angiogram after admission. MVD was defined as coronary lesions with ≥50% diameter stenosis by quantitative coronary analysis in the left main coronary artery or three major coronary arteries[22].

Definition of other variables

We defined hypertension as having a history of hypertension, receiving antihypertensive therapy or systolic blood pressure 140 mmHg or diastolic blood pressure ≥90 mmHg at admission. Elevated total cholesterol was defined as serum total

cholesterol ≥6.2 mmol/L. Low high-density lipoprotein cholesterol was defined as serum high-density lipoprotein cholesterol <1.0 mmol/L. Elevated triglyceride (TG) was defined as serum triglyceride ≥2.3 mmol/L. Hyperlipidemia was defined as an elevation of total cholesterol and/or triglyceride or low high-density lipoprotein cholesterol. Current smoking was defined as smoking in the preceding 1 year, according to the medical records of the patients.

Statistical analysis

Continuous and categorical variables were presented as medians (standard deviation) and as frequencies (%), respectively. Student's *t*-test was used for comparison of continuous variables, whereas the χ^2-test was used for comparison of categorical variables.

We first examined the associations between diabetes mellitus and CAD extent and severity. Ordinal logistic regression was used to estimate the odds ratios (ORs) of higher Killip class. A full likelihood ratio test showed that the proportional odds assumption was satisfied. Unconditional logistic regression was used to estimate the ORs of admission tachycardia and MVD. The association between HbA1c and CAD extent and severity was then analyzed by using the same models. HbA1c was evaluated as a continuous variable and a categorical variable based on quartiles in separate models. When we investigate the effect of glycemic control in diabetes mellitus patients, HbA1c was categorized according to general HbA1c goals. The analysis was further stratified by hypertension and hyperlipidemia. Multiplicative interaction was tested by using a likelihood ratio test comparing models with and without cross-product terms.

Crude and multivariate-adjusted ORs, with accompanying 95% confidence intervals (CIs), were reported for the respective categories, in comparison with the referent group of patients. The models were adjusted for measured covariates, which included sex, age groups, body mass index group, smoking status, hypertension, hyperlipidemia, history of prior MI, PCI or coronary artery bypass grafting and history of cerebral vascular disease. A *P*-value <0.05 was considered statistically significant. All statistical analyses were carried out using SAS software (version 9.4 [USA version]; SAS Institute, Cary, NC, USA).

RESULTS

Patient characteristics

We divided a total of 8,370 patients into two groups, the diabetes mellitus (n = 3,398) and the non-diabetes mellitus group (n = 4,972). Patients with diabetes mellitus were older, more likely to be female and overweight, but less likely to be current/recent smokers. More patients in the diabetes mellitus group had a history of MI, PCI, peripheral arterial disease, cerebrovascular disease, heart failure, hypertension and dyslipidemia in comparison with the non-diabetes mellitus group. Table 1 summarizes the baseline characteristics of STEMI patients in different groups.

Diabetes mellitus HbA1c values, and CAD extent and severity

Compared with non-diabetes patients, diabetes patients were at an increased risk of more severe STEMI. After multivariable adjustment, the ORs were 1.12 (95% CI 1.01–1.25) for higher Killip class, 1.40 (95% CI 1.21–1.61) for tachycardia and 1.42 (95% CI 1.27–1.58) for MVD for diabetes patients. HbA1c value was also significantly related to tachycardia (OR 1.11 per 1% HbA1c increment, 95% CI 1.07–1.15) and MVD (OR 1.11 per 1% HbA1c increment, 95% CI 1.07–1.15; Table 2).

HbA1c quartiles, and CAD extent and severity

The relationship between HbA1c levels and CAD extent and severity was different in patients with and without diabetes (Table 3). When non-diabetes mellitus patients were divided into four groups according to HbA1c interquartile range (group 1, <5.4% [<36 mmol/mol]; group 2, 5.4–5.6% [36–38 mmol/mol]; group 3, 5.6–5.9% [38–41 mmol/mol]; and group 4, >5.9% [>41 mmol/mol]), HbA1c >5.9% was significantly associated with the risk of higher Killip class and MVD; however, in multivariable analyses, these associations lost statistical significance. We also divided diabetes patients into four groups according to HbA1c interquartile range (group 1, <6.8% [<51 mmol/mol]; group 2, 6.8–7.7% [51–61 mmol/mol]; group 3, 7.7–9.2% [61–77 mmol/mol]; and group 4, >9.2% [>77 mmol/mol]), using non-diabetes mellitus patients with an HbA1c <5.4% as reference group. For higher Killip class, the risks were not significantly different between non-diabetes mellitus and diabetes mellitus patients. For tachycardia, patients in group 3 (OR 1.40, 95% CI 1.12–1.75) and group 4 (OR 1.78, 95% CI 1.44–2.20) had significantly increased risk. For MVD, all the groups showed higher risk of MVD in comparison with the non-diabetes mellitus group.

HbA1c targets, and CAD extent and severity in patients with diabetes

We further chose HbA1c levels of 6.5 and 7% as cut-off points in diabetes patients, because they are standard HbA1c targets in clinical practice among patients receiving therapy for diabetes[23] (group 1, ≤6.5% [<48 mmol/mol]; group 2, 6.5–7.0% [48–53 mmol/mol]; and group 3, ≥7.0% [>53 mmol/mol]; Table 4). The non-diabetes mellitus group was defined as the reference group as before. In the multivariable logistic models for higher Killip class, the ORs for diabetes patients were insignificant except for group 3 (OR 1.14, 95% CI 1.01–1.29). For tachycardia, low HbA1c level (HbA1c <6.5%, OR 1.33, 95% CI 1.00–1.76) and high HbA1c level (HbA1c >7.0%, OR 1.50, 95% CI 1.28–1.75) were associated with significantly higher risk. All the HbA1c categories in diabetes mellitus patients were associated with a 1.30–1.49-fold increased risk of MVD after multivariable adjustments.

We also carried out secondary analyses stratified by hypertension and hyperlipidemia (Tables 5,6, all $P > 0.05$ for interactions). When stratifying into the hypertension and non-hypertension group, no statistically significant association was

Table 1 | Baseline characteristics among the non-diabetes mellitus group versus the diabetes mellitus group

	Non-DM (n = 4,972)	DM (n = 3,398)	Total (n = 8,370)	P-value
Demographic and prior clinical history				
Age (years)	62.32 ± 11.92	60.91 ± 13.13	61.49 ± 12.67	<0.001
Male sex	4,091 (82.33)	2,544 (74.87)	6,635 (79.30)	<0.001
BMI >25	1,948 (39.18)	1,595 (46.94)	3,543 (42.33)	<0.001
Current smoking	2,678 (53.92)	1,555 (45.8)	4,233 (50.62)	<0.001
Prior MI	218 (4.39)	217 (6.39)	435 (5.21)	<0.001
Prior PCI	192 (3.87)	224 (6.60)	416 (4.98)	<0.001
Prior CABG	7 (0.14)	9 (0.27)	16 (0.19)	0.201
Peripheral arterial disease	74 (1.49)	81 (2.39)	155 (1.86)	0.003
Cerebrovascular disease	422 (8.55)	388 (11.53)	810 (9.76)	<0.001
Prior heart failure	21 (0.42)	39 (1.15)	60 (0.72)	<0.001
Metabolic characteristics at admission				
HbA1c (%)	5.61 ± 0.53	8.12 ± 1.82	6.63 ± 1.74	<0.001
Hypertension	2,448 (49.30)	2,074 (61.11)	4,522 (54.09)	<0.001
Systolic blood pressure (mmHg)	128.65 ± 33.64	130.74 ± 25.16	129.50 ± 30.50	0.002
Diastolic blood pressure (mmHg)	79.13 ± 16.09	79.03 ± 16.03	79.09 ± 16.06	0.790
Dyslipidemia	2,211 (44.59)	1,783 (52.55)	3,994 (47.82)	<0.001
Total cholesterol (mmol/L)	4.82 ± 7.49	4.77 ± 1.68	4.80 ± 5.90	0.773
Triglycerides (mmol/L)	2.04 ± 18.5	2.09 ± 2.45	2.06 ± 14.45	0.907
HDL-C (mmol/L)	1.15 ± 0.42	1.12 ± 2.09	1.14 ± 1.36	0.538
LDL-C (mmol/L)	3.04 ± 0.98	3.03 ± reference	3.04 ± 0.99	0.788
Clinical characteristics at admission				
Killip classification				
I	3,763 (76.97)	2,471 (73.89)	6,234 (75.72)	0.001
II	725 (14.83)	559 (16.72)	1,284 (15.60)	
III	166 (3.40)	158 (4.72)	324 (3.94)	
IV	235 (4.81)	156 (4.67)	391 (4.75)	
Heart rate (b.p.m.)	77.53 ± 16.60	79.81 ± 17.42	78.45 ± 16.97	<0.001
No. stenosed vessel				
1 vessel	1,257 (25.28)	642 (18.89)	1,899 (22.69)	<0.001
2 vessels	1,079 (21.70)	676 (19.89)	1,755 (20.97)	
≥3 vessels	1,120 (22.52)	938 (27.61)	2,058 (24.59)	
LMS	180 (3.62)	146 (4.30)	326 (3.89)	
No performed CAG	1,336 (26.87)	996 (29.31)	2,332 (27.86)	

BMI, body mass index; CABG, coronary artery bypass grafting; CAG, coronary angiogram; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; TG, triglyceride.

found between the HbA1c level and higher Killip class across the strata. For non-hypertensive patients, the ORs for tachycardia and MVD were significant only for HbA1c >7.0%. For hypertensive patients, by contrast, the ORs for tachycardia were significant for HbA1c ≤6.5% (OR 1.46, 95% CI 1.04–2.05) and HbA1c >7% (OR 1.47, 95% CI 1.19–1.82). In the fully adjusted multivariable logistic models for MVD, the ORs compared with non-diabetes patients were 1.41 (95% CI 1.08–1.86) for HbA1c ≤6.5%, 1.32 (95% CI 1.03–1.70) for HbA1c between 6.5 and 7.0%, and 1.44 (95% CI 1.22–1.70) for HbA1c >7.0%.

For patients without hyperlipidemia, HbA1c categories >6.5% were associated with a 1.29–1.39 fold increased risk of MVD. For hyperlipidemia patients, the adjusted ORs compared with non-diabetes patients were 1.57 (95% CI 1.17–2.12) for HbA1c ≤6.5%, 1.22 (95% CI 0.93–1.61) for HbA1c between 6.5 and 7.0%, and 1.68 (95% CI 1.42–1.99) for HbA1c >7.0%.

DISCUSSION

In the present study of 8,000 patients admitted with a STEMI across China, we found that diabetes mellitus and HbA1c levels were associated with the extent and severity of CAD. For patients with diabetes mellitus, especially those comorbid with hypertension or hyperlipidemia, HbA1c below generally recommended levels might still increase the risk of CAD progression.

Using HbA1c for the diagnosis of diabetes mellitus has several strengths, it measures the average plasma glucose level over 2–3 months, is largely unaffected by acute illness and could be used to guide management[24]. Simultaneously, clinical features selected in the present study not only represent the cardiac

Table 2 | Association between diabetes mellitus, glycosylated hemoglobin values and coronary artery disease extent and severity

Variable	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Higher Killip class				
DM (no/yes)†	1.18 (1.07–1.30)	0.001	1.12 (1.01–1.25)	0.035
HbA1c (%)‡	1.01 (0.98–1.04)	0.386	1.01 (0.98–1.04)	0.649
Admission tachycardia				
DM (no/yes)†	1.40 (1.22–1.61)	<0.001	1.40 (1.21–1.61)	<0.001
HbA1c (%)‡	1.11 (1.07–1.15)	<0.001	1.11 (1.07–1.15)	<0.001
MVD				
DM (no/yes)†	1.48 (1.33–1.64)	<0.001	1.42 (1.27–1.58)	<0.001
HbA1c (%)‡	1.11 (1.08–1.15)	<0.001	1.11 (1.07–1.15)	<0.001

†Diabetes mellitus (DM) was used as a categorical variable, whereas the non-DM group was used as the reference group. Multivariate analysis adjusted for sex, age, body mass index, smoking status, hypertension, hyperlipidemia, history of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting and history of cerebral vascular disease. ‡Glycosylated hemoglobin (HbA1c) value was used as a continuous variable. Multivariate analysis adjusted for sex, age, body mass index, smoking status, hypertension, hyperlipidemia, history of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting and history of cerebral vascular disease. CI, confidence interval; MVD, multi-vessel coronary artery disease; OR, odds ratio.

damage and systemic change in STEMI, but also have considerable prognostic value. AHR and Killip classification are both univariate and multivariate predictors of poor prognosis after MI[2,3,25]. Whereas MVD has been proved to be a strong risk factor for recurrent cardiovascular events in a long-term nationwide study[26]. The different associations between these clinical features with HbA1c might also show their sensitivity in the progression of CAD.

Table 3 | Odds ratios of coronary artery disease extent and severity according to glycosylated hemoglobin interquartiles

Variable	HbA1c interquartiles			
Non-DM group	HbA1c < 5.4 (*n* = 1,153)	5.4 ≤ HbA1c ≤ 5.6 (*n* = 1,346) OR (95% CI)	5.6 < HbA1c ≤ 5.9 (*n* = 1,345) OR (95% CI)	HbA1c >5.9 (*n* = 1,128) OR (95% CI)
Higher Killip class				
Univariate	Reference	0.96 (0.79–1.16)	0.97 (0.80–1.17)	1.29 (1.07–1.56)†
Multivariate‡	Reference	0.91 (0.75–1.05)	0.86 (0.71–1.05)	1.16 (0.96–1.41)
Admission tachycardia				
Univariate	Reference	0.83 (0.63–1.09)	0.86 (0.65–1.12)	1.11 (0.85–1.46)
Multivariate‡	Reference	0.85 (0.65–1.12)	0.89 (0.68–1.17)	1.16 (0.88–1.53)
MVD				
Univariate	Reference	1.02 (0.84–1.24)	1.11 (0.91–1.35)	1.26 (1.03–1.54)†
Multivariate‡	Reference	0.96 (0.79–1.18)	1.00 (0.82–1.22)	1.13 (0.92–1.39)
DM group	HbA1c <6.8 (*n* = 808) OR (95% CI)	6.8 ≤ HbA1c < 7.7 (*n* = 862) OR (95% CI)	7.7 ≤ HbA1c < 9.2 (*n* = 874) OR (95% CI)	HbA1c ≥9.2 (*n* = 854) OR (95% CI)
Higher Killip class				
Univariate	1.29 (1.05–1.59)†	1.20 (0.98–1.47)	1.37 (1.12–1.68)†	1.06 (0.86–1.31)
Multivariate‡	1.11 (0.96–1.36)	1.07 (0.90–1.27)	1.24 (1.05–1.46)	1.05 (0.88–1.25)
Admission tachycardia				
Univariate	1.16 (0.87–1.55)	1.11 (0.84–1.45)	1.31 (0.99–1.73)	1.70 (1.30–2.21)†
Multivariate‡	1.22 (0.96–1.56)	1.20 (0.95–1.53)	1.40 (1.12–1.75)†	1.78 (1.44–2.20)†
MVD				
Univariate	1.55 (1.25–1.93)†	1.47 (1.19–1.82)†	1.61 (1.30–2.00)†	1.86 (1.49–2.31)†
Multivariate‡	1.33 (1.11–1.60)†	1.22 (1.02–1.46)†	1.43 (1.20–1.71)†	1.75 (1.46–2.10)†

†Statistically significant, $P < 0.05$. ‡Multivariate analysis adjusted for sex, age, body mass index, smoking status, hypertension, hyperlipidemia, history of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting and history of cerebral vascular disease. CI, confidence interval; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MVD, multi-vessel coronary artery disease; OR, odds ratio.

Table 4 | Odds ratios of coronary artery disease extent and severity according to glycosylated hemoglobin targets in diabetes mellitus group

Variable	Non-DM (n = 4,972)	HbA1c ≤6.5 (n = 533) OR (95% CI)	6.5 < HbA1c ≤ 7 (n = 623) OR (95% CI)	HbA1c >7 (n = 2,242) OR (95% CI)
Higher Killip class				
Univariate	Reference	1.19 (0.97–1.46)	1.12 (0.93–1.36)	1.19 (1.06–1.34)†
Multivariate‡	Reference	1.08 (0.87–1.33)	1.08 (0.89–1.32)	1.14 (1.01–1.29)†
Admission tachycardia				
Univariate	Reference	1.35 (1.03–1.78)†	1.08 (0.82–1.43)	1.50 (1.29–1.75)†
Multivariate‡	Reference	1.33 (1.00–1.76)†	1.13 (0.85–1.49)	1.50 (1.28–1.75)†
MVD				
Univariate	Reference	1.38 (1.11–1.70)†	1.41 (1.15–1.71)†	1.53 (1.35– 1.72)†
Multivariate‡	Reference	1.30 (1.05–1.62)†	1.29 (1.05–1.57)†	1.49 (1.31–1.68)†

†Statistically significant, $P < 0.05$. ‡Multivariate analysis adjusted for sex, age, body mass index, smoking status, hypertension, hyperlipidemia, history of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting and history of cerebral vascular disease. CI, confidence interval; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MVD, multi-vessel coronary artery disease; OR, odds ratio.

The association between diabetes mellitus and CAD severity has been studied in previous populations. In patients from the contemporary Euro Heart Survey PCI Registry[27] undergoing elective or emergency PCI, diabetes mellitus was found to be related to more frequent cardiogenic shock, more severely stenosed (≥70%) segments and more frequent comorbidities. In a more recent study of 23,643 consecutive individuals undergoing coronary computed tomography angiography[28], compared with non-diabetes mellitus individuals, the extent of obstructive CAD was higher among diabetes mellitus patients, with higher per-segment stenosis in the proximal and mid-segments of every coronary artery.

HbA1c level has been studied in both non-diabetic and diabetic CAD patients previously. In non-diabetic CAD patients, conflicting findings exist on the relationship between HbA1c level and CAD severity. Hong *et al.*[11], Cai *et al.*[29] and Ashraf *et al.*[30]. found high HbA1c level to be associated with more vessel stenosis, whereas Wang *et al.*[12]. showed opposite

Table 5 | Odds ratios of coronary artery disease extent and severity according to glycosylated hemoglobin targets in diabetes mellitus patient, by hypertension

Variable	Non-DM (n = 4,972)	HbA1c ≤6.5 (n = 533) OR (95% CI)	6.5 < HbA1c ≤ 7 (n = 623) OR (95% CI)	HbA1c >7 (n = 2,242) OR (95% CI)
Non-hypertension group				
Higher Killip class				
Univariate	Reference	1.05 (0.73–1.50)	1.35 (0.99–1.83)	1.23 (1.03–1.47)†
Multivariate‡	Reference	1.04 (0.72–1.49)	1.29 (0.94–1.75)	1.17 (0.98–1.41)
Admission tachycardia				
Univariate	Reference	1.06 (0.64–1.76)	1.37 (0.90–2.08)	1.50 (1.18–1.90)†
Multivariate‡	Reference	1.09 (0.66–1.82)	1.41 (0.93–2.16)	1.53 (1.20–1.94)†
MVD				
Univariate	Reference	1.12 (0.78–1.60)	1.37 (0.99–1.90)	1.64 (1.36–1.97)†
Multivariate‡	Reference	1.09 (0.76–1.58)	1.23 (0.88–1.71)	1.56 (1.29–1.88)†
Hypertension group				
Higher Killip class				
Univariate	Reference	1.22 (0.95–1.56)	0.98 (0.77–1.26)	1.14 (0.98–1.33)
Multivariate‡	Reference	1.10 (0.85–1.43)	0.98 (0.76–1.27)	1.13 (0.96–1.32)
Admission tachycardia				
Univariate	Reference	1.46 (1.05–2.05)†	0.92 (0.63–1.33)	1.50 (1.22–1.84)†
Multivariate‡	Reference	1.46 (1.04–2.05)†	0.96 (0.66–1.40)	1.47 (1.19–1.82)†
MVD				
Univariate	Reference	1.45 (1.11–1.89)†	1.34 (1.04–1.72)†	1.39 (1.18–1.63)†
Multivariate‡	Reference	1.41 (1.08–1.86)†	1.32 (1.03–1.70)†	1.44 (1.22–1.70)†

†Statistically significant, $P < 0.05$. ‡Multivariate analysis adjusted for sex, age, body mass index, smoking status, hypertension, hyperlipidemia, history of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting and history of cerebral vascular disease. CI, confidence interval; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MVD, multi-vessel coronary artery disease; OR, odds ratio.

Table 6 | Odds ratios of coronary artery disease extent and severity according to glycosylated hemoglobin targets in diabetes mellitus patient, by hyperlipidemia

Variable	Non-DM (n = 4,972)	HbA1c ≤6.5 (n = 533) OR (95% CI)	6.5 < HbA1c ≤ 7 (n = 623) OR (95% CI)	HbA1c >7 (n = 2,242) OR (95% CI)
Non-hyperlipidemia group				
Higher Killip class				
Univariate	Reference	1.27 (0.96–1.67)	1.12 (0.85–1.47)	1.36 (1.16–1.59)†
Multivariate‡	Reference	1.14 (0.85–1.51)	1.06 (0.80–1.41)	1.29 (1.09–1.52)†
Admission tachycardia				
Univariate	Reference	1.28 (0.86–1.91)	1.38 (0.95–2.02)	1.77 (1.42–2.19)†
Multivariate‡	Reference	1.29 (0.86–1.94)	1.43 (0.98–2.09)	1.73 (1.39–2.16)†
MVD				
Univariate	Reference	1.20 (0.88–1.63)	1.50 (1.12–2.00)†	1.33 (1.11–1.60)†
Multivariate‡	Reference	1.05 (0.77–1.46)	1.39 (1.04–1.87)†	1.29 (1.07–1.55)†
Hyperlipidemia group				
Higher Killip class				
Univariate	Reference	1.09 (0.80–1.48)	1.16 (0.89–1.53)	1.08 (0.91–1.27)
Multivariate‡	Reference	1.01 (0.73–1.38)	1.11 (0.84–1.47)	1.01 (0.84–1.20)
Admission tachycardia				
Univariate	Reference	1.40 (0.96–2.05)	0.85 (0.56–1.29)	1.30 (1.05–1.63)†
Multivariate‡	Reference	1.36 (0.92–2.01)	0.87 (0.57–1.31)	1.28 (1.02–1.60)†
MVD				
Univariate	Reference	1.60 (1.20–2.15)†	1.38 (1.05–1.80)†	1.75 (1.49–2.06)†
Multivariate‡	Reference	1.57 (1.17–2.12)†	1.22 (0.93–1.61)	1.68 (1.42–1.99)†

†Statistically significant, $P < 0.05$. ‡Multivariate analysis adjusted for sex, age, body mass index, smoking status, hypertension, hyperlipidemia, history of prior myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting and history of cerebral vascular disease. CI, confidence interval; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; MVD, multi-vessel coronary artery disease; OR, odds ratio.

findings. We found non-diabetes mellitus patients with an HbA1c >5.9% were at increased risk of higher Killip class and MVD; however, the relationship did not remain significant after multivariable adjustments, indicating the patients in the HbA1c >5.9% group might be more comorbid compared with the other HbA1c groups. In diabetes patients, although data in STEMI patients remain scarce in the literature, HbA1c level was shown to be related to the severity and complexity of coronary lesions[31]. The results of the present study confirmed the positive relationship toward the progression of CAD for diabetes mellitus patients for HbA1c level.

In light of the present findings, we suggest that an HbA1c ≤6.5% might fail to halt the progression of CAD, especially for diabetes patients with hypertension or hyperlipidemia. The Kumamoto Study[32] and UK Prospective Diabetes Study[33] confirmed that lowering HbA1c from 7% to 6% is associated with a significant reduction in microvascular complications in diabetes mellitus patients. However, three large trials in 2008 suggested CAD outcomes were not significantly reduced with intensive glycemic control in participants followed for 3.5–5.6 years[34]. It is notable that all three trials were carried out in relatively older participants with longer known duration of diabetes mellitus (mean duration 8–11 years). There is evidence that more intensive treatment of glycemia in newly diagnosed patients might reduce long-term CVD rates[14]. After a 10-year observational follow up of UK Prospective Diabetes Study, those originally randomized to intensive glycemic control had significant long-term reductions in MI and all-cause mortality (13% and 27%, respectively)[35]. Therefore, we support the latest edition of the European Society of Cardiology and the European Association for the Study of Diabetes diabetes treatment guidelines that intensive secondary prevention and a more stringent HbA1c target should be considered for diabetes patients, particularly for those with CAD and other comorbidities[36].

In the present study population of patients with STEMI, HbA1c might be both a marker of risk and potentially also related to the pathophysiological mechanism. Evidence shows that atherosclerotic build-up begins well before the onset of clinical diabetes mellitus symptoms, and cardiac outcomes are significantly worsened in the presence of diabetes mellitus[37]. Worse left ventricular function, larger infarct size and increases in serum biomarkers of inflammation might further promote the development of secondary cardiac arrhythmias and heart failure[38]. Although no interaction was observed between hypertension, hyperlipidemia and diabetes mellitus, other mechanisms might be in play. Several studies have been proposed to clarify the underlying mechanisms of the synergistic effects of the three abnormalities, even in their early stage, on the accelerated progression of arteriosclerotic arterial damage[39–41]. As the latest American Diabetes Association emphasized[23], comorbidities may decrease the potential to reap benefits from intensive glycemic control. Thus, HbA1c

targets must be individualized based on key patient characteristics.

Potential limitations inherent to the nature of real-world studies are present. First, there is a lack of information about the duration of hyperlipidemia, hypertension and diabetes mellitus. Thus, we cannot rule out the effect of unmeasured confounders while estimating the effect of diabetes mellitus and comorbidity. Furthermore, we have only one measurement of HbA1c; therefore, the variations in the control of glycemic parameters are unknown. We might have a more significant correlation with CAD progression if we had average measurements. Finally, only in-hospital information is available in the present study, and long-term follow up could not be assessed. Therefore, more advanced methodologies, such as cohort studies, are recommended.

In conclusion, we examined the relationship between HbA1c levels and CAD extent and severity in 8,370 consecutive STEMI patients admitted from 2015 to 2017 across China. HbA1c below generally recommended levels might fail to halt the progression of CAD, especially for diabetes mellitus patients with comorbid hypertension or hyperlipidemia. Thus, for post-MI patients with diabetes mellitus and other comorbidities, physicians might use the number of stenosed vessels to improve cardiovascular risk assessment, and consider more intensive and individually tailored glycemic control.

ACKNOWLEDGMENTS

The authors thank the China STEMI Care Project-2 study team members and all those who participated in the study. They also appreciate the organizational coordination of the Chinese Medical Doctor Association and China Cardiovascular Association, and support from the National Health Commission and local governments in China.

DISCLOSURE

The authors declare no conflict of interest, but report that Chinese Medical Doctor Association with support from AstraZeneca, Abbott, Sanofi-Aventis, Essen Technology (Beijing) Co., Ltd., Shenzhen Salubris Pharmaceuticals Co., Ltd., Lepu Medical Technology (Beijing) Co., Ltd. and Tasly Pharmaceutical Group Co., Ltd. supported the China STEMI Care Project-2 study. This work was also supported in part by the National Natural Science Foundation of China (No. 81872692) and the Beijing Municipal Natural Science Foundation (No. 7182085). None of the funding agencies were involved in the study design, data collection, data analysis, manuscript preparation or publication decisions.

REFERENCES

1. Aronson D, Edelman ER. Coronary artery disease and diabetes mellitus. *Cardiol Clin* 2014; 32: 439–455.
2. Jensen MT, Pereira M, Araujo C, *et al*. Heart rate at admission is a predictor of in-hospital mortality in patients with acute coronary syndromes: results from 58 European hospitals: the European Hospital Benchmarking by Outcomes in acute coronary syndrome Processes study. *Eur Heart J Acute Cardiovasc Care* 2018; 7: 149–157.
3. El-Menyar A, Zubaid M, Almahmeed W, *et al*. Killip classification in patients with acute coronary syndrome: insight from a multicenter registry. *Am J Emerg Med* 2012; 30: 97–103.
4. Yusuf S, Zucker D, Peduzzi P, *et al*. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; 344: 563–570.
5. Mark DB, Nelson CL, Califf RM, *et al*. Continuing evolution of therapy for coronary artery disease. Initial results from the era of coronary angioplasty. *Circulation* 1994; 89: 2015–2025.
6. Nauta ST, Deckers JW, Martijn AK, *et al*. Short- and long-term mortality after myocardial infarction in patients with and without diabetes. *Diabetes Care* 2012; 35: 2043–2047.
7. Low Wang CC, Hess CN, Hiatt WR, *et al*. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus – mechanisms, management, and clinical considerations. *Circulation* 2016; 133: 2459–2502.
8. American Diabetes Association. 5. Glycemic targets. *Diabetes Care* 2016; 39(Suppl 1): S39–S46.
9. Ikeda N, Iijima R, Hara H, *et al*. Glycated hemoglobin is associated with the complexity of coronary artery disease, even in non-diabetic adults. *J Atheroscler Thromb* 2012; 19: 1066–1072.
10. Chen CL, Yen HT, Lin CS, *et al*. Glycated hemoglobin level is an independent predictor of major adverse cardiac events after nonfatal acute myocardial infarction in nondiabetic patients. *Medicine* 2017; 96: e6743.
11. Hong LF, Li XL, Guo YL, *et al*. Glycosylated hemoglobin A1c as a marker predicting the severity of coronary artery disease and early outcome in patients with stable angina. *Lipids Health Dis* 2014; 13: 1–9.
12. Xinhong W, Zhenhua H, Guanghua H, *et al*. Hemoglobin A1c level is not related to the severity of atherosclerosis in patients with acute coronary syndrome. *Dis Markers*. 2015; 2015: 1–5.
13. Radovanovic D, Seifert B, Urban P, *et al*. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002–2012. *Heart* 2014; 100: 288–294.
14. Gaede P, Lund-Andersen H, Parving HH, *et al*. Effect of a multifactorial intervention on mortality in type II diabetes. *J Vasc Surg* 2008; 47: 1371.
15. Gaede P, Vedel P, Larsen N, *et al*. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *N Engl J Med* 2003; 348: 383–393.
16. Melle JPV, Bot M, Jonge PD, *et al*. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease data from the heart and soul study. *Diabetes Care* 2010; 33: 2084–2089.

17. Pavlicek V. Risk factors and cardiovascular outcomes in patients with type 2 diabetes mellitus. *Diabetologe* 2018; 14: 499–500.
18. Thygesen K, Alpert JS, Jaffe AS, *et al*. Third universal definition of myocardial infarction. *Circulation* 2012; 126: 2020–2035.
19. Chinese Society of Cardiology, Editorial board of Chinese Journal of Cardiology. Guidelines for the diagnosis and treatment of acute ST segment elevation myocardial infraction. *Chin J Cardiol*. 2015; 43: 380–393 (Chinese).
20. Zhang Y, Yu B, Han Y, *et al*. Protocol of the China ST-segment elevation myocardial infarction (STEMI) Care Project (CSCAP): a 10-year project to improve quality of care by building up a regional STEMI care network. *BMJ Open* 2019; 9: e026362.
21. Khot UN, Jia G, Moliterno DJ, *et al*. Prognostic importance ofphysical examination for heart failure in non–ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA* 2003; 290: 2174–2181.
22. Shishehbor MH, Lauer MS, Singh IM, *et al*. In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culpritonly stenting. *J Am Coll Cardiol* 2007; 49: 849–854.
23. ADA. Glycemic targets: standards of medical care in diabetes-2019. *Diabetes Care* 2019; 41(Suppl 1): S61–S70.
24. Jeffcoate SL. Diabetes control and complications: the role of glycated haemoglobin, 25 years on. *Diabet Med* 2004; 21: 657–665.
25. Parakh K, Thombs BD, Bhat U, *et al*. Long-term significance of killip class and left ventricular systolic dysfunction. *Am J Med* 2008; 121; 1015–1018.
26. Özcan C, Deleskog A, Schjerning Olsen A-M, *et al*. Coronary artery disease severity and long-term cardiovascular risk in patients with myocardial infarction: a Danish nationwide register-based cohort study. *Eur Heart J Cardiovasc Pharmacother* 2018; 4: 25–35.
27. Timm Bauer MD, Helge Möllmann MD, Franz Weidinger MD, *et al*. Impact of diabetes mellitus status on coronary pathoanatomy and interventional treatment: insights from the Euro heart survey PCI registry. *Catheter Cardiovasc Interv* 2011; 78: 702–709.
28. Rana J, Dunning A, Achenbach S, *et al*. Differences in prevalence, extent, severity, and prognosis of coronary artery disease among patients with and without diabetes undergoing coronary computed tomography angiography: results from 10,110 individuals from the confirm (COronary CT Angiography EvaluatioN For Clinical Outcomes): an InteRnational Multicenter Registry. *Diabetes Care* 2012; 35: 1787–1794.
29. Cai A, Li G, Chen J, *et al*. Glycated hemoglobin level is significantly associated with the severity of coronary artery disease in non-diabetic adults. *Lipids Health Dis* 2014; 13: 181.
30. Ashraf H, Boroumand MA, Amirzadegan A, *et al*. Hemoglobin A1C in non-diabetic patients: an independent predictor of coronary artery disease and its severity. *Diabetes Res Clin Pract* 2013; 102: 908–916.
31. Ma J, Wang X, Wang Y, *et al*. The relationship between glycated hemoglobin and complexity of coronary artery lesions among older patients with diabetes mellitus. *PLoS ONE* 2014; 9: 1–5.
32. Ohkubo Y, Kishikawa H, Araki E, *et al*. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995; 28: 103–117.
33. Listed N. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352; 854–865.
34. Bloomgarden ZT. Glycemic control in diabetes: a tale of three studies. *Diabetes Care* 2008; 31: 1913–1919.
35. Holman RR, Paul SK, Bethel MA, *et al*. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359: 1577–1589.
36. Cosentino F, Grant PJ, Aboyans V, *et al*. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J* 2019; 34: 3035–3087.
37. Buring JE. Risk markers and the primary prevention of cardiovascular disease. In: Ridker PMLP, Buring JE, Ridker PM, Libby P, Inc E (eds). Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. Philadelphia, PA: Elsevier/ Saunders, 2015; 891–933.
38. Tran HV, Gore JM, Darling CE, *et al*. Hyperglycemia and risk of ventricular tachycardia among patients hospitalized with acute myocardial infarction. *Cardiovasc Diabetol* 2018; 17: 1–9.
39. Wang X, Desai K, Chang T, *et al*. Vascular methylglyoxal metabolism and the development of hypertension. *J Hypertens* 2005; 23: 1565–1573.
40. Masoudkabir F, Poorhosseini H, Vasheghani-Farahani A, *et al*. Synergistic effect of hypertension with diabetes mellitus and gender on severity of coronary atherosclerosis: findings from Tehran heart center registry. *ARYA Atheroscle* 2015; 11: 1–6.
41. Sorop O, van den Heuvel M, van Ditzhuijzen NS, *et al*. Coronary microvascular dysfunction after long-term diabetes and hypercholesterolemia. *Am J Physiol Heart Circ Physiol* 2016; 311: H1339–H1351.