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

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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 STEMICare 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. 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. Coronary angiogram has long been the gold standard for evaluation of CAD, while the number of
stened 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\(^16,19\). 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 multi-vessel 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 (Abbott 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 \(\geq 6.5\% \) (\(\geq 48\) 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 \(\geq 90\) mmHg; class III patients had pulmonary edema with rales involving more than one-third of the posterior lung fields and systolic blood pressure of \(\geq 90\) 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 \(\geq 100\) 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 \(\geq 50\%\) 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 \(\geq 90\) 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 current 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 χ²-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 ≥5.4% 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 diabetes23 (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                       | 4091 (82.33)       | 2544 (74.87)   | 6625 (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  |
| Dyslipidemia                   | 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   |
| Systolic blood pressure (mmHg) | 2,211 (44.59)      | 1,783 (52.55)  | 3,994 (47.32)     | <0.001  |
| Total cholesterol (mmol/L)     | 482 ± 7.49         | 477 ± 6.68     | 480 ± 5.90        | 0.773   |
| Triglycerides (mmol/L)         | 204 ± 18.5         | 209 ± 2.45     | 206 ± 14.45       | 0.907   |
| HDL-C (mmol/L)                 | 1.15 ± 0.04        | 1.12 ± 0.20    | 1.14 ± 0.36       | 0.538   |
| LDL-C (mmol/L)                 | 3.04 ± 0.98        | 3.03 ± reference| 3.04 ± 0.99       | 0.788   |
| 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 (25.28)      | 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. 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.

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

| Variable                  | HbA1c interquartiles |            |           |             |               |           |               |
|---------------------------|----------------------|------------|-----------|-------------|---------------|-----------|---------------|
|                           | HbA1c < 5.4 (n = 1,153) | 5.4 ≤ HbA1c ≤ 5.6 (n = 1,346) | 5.6 ≤ HbA1c ≤ 5.9 (n = 1,345) | HbA1c >5.9 (n = 1,128) |            |           |               |
|                           | OR (95% CI)          | OR (95% CI) | OR (95% CI) | 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 angiography30, 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.,90 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 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. 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 Study32 and UK Prospective Diabetes Study33 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, 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.

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DISCLOSURE

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