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Glycosylated hemoglobin levels and clinical outcomes in nondiabetic patients with coronary artery disease
A meta-analysis

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Abstract

A number of studies assessed the prognostic value of HbA1c level in nondiabetic patients with coronary artery disease (CAD). The purpose of this meta-analysis was to assess the association between the HbA1c level and clinical outcomes.

We searched PubMed, EMBASE, MEDLINE, and the Cochrane Library from their inception to 10 April 2016. Studies evaluated the outcomes according to HbA1c levels in CAD patients without diabetes mellitus were eligible.

Twenty studies involving 22,428 patients were included. In nondiabetic patients with CAD, a high HbA1c level was associated with a higher rate of long-term death (odds ratio 1.76, 95% confidence interval 1.44–2.16, $P < .001$), and myocardial infarction (MI, odds ratio 1.69, 95% confidence interval 1.07–2.67, $P = .026$), but not a higher rate of early deaths (odds ratio 1.08, 95% confidence interval 0.92–1.27, $P = .359$). These findings for death remained the same after sensitivity analyses and the trim and fill method, but the risk difference for MI became nonsignificant after adjustment for potential publication bias.

Elevated HbA1c level increased the risks of long-term mortality and MI, but not the risk for early deaths in nondiabetic patients with CAD. High-quality large-scale studies with less bias are needed to confirm these findings.

Abbreviations: AMI = acute myocardial infarction, CAD = coronary artery disease, CI = confidence interval, DM = diabetes mellitus, HbA1c = glycated hemoglobin, OR = odds ratio.

Keywords: coronary artery disease, glycosylated hemoglobin, mortality, myocardial infarction, prediabetes

1. Introduction

Acute glycemic disorder, indicated by a high plasma glucose level, is a powerful predictor of prognosis in patients with acute myocardial infarction (AMI) but without diabetes mellitus (DM).[1,2] Increased glucose level may suggest previously undiagnosed DM[3]; however, the glycemic test is rarely used to diagnose diabetes in patients encountering AMI because the glucose level could increase at the acute phase of cardiac events in all patients.[4,5] Glycated hemoglobin (HbA1c), reflecting the average blood glucose level of the past 2 to 3 months, is a well-known biomarker of long-term glycometabolic control[6] and is also recommended in the diagnosis of DM since 2010.[7] Previous studies demonstrated that the HbA1c level was significantly associated with all-cause mortality in nondiabetic patients with coronary artery disease (CAD).[8–13] Subgroup analysis of a meta-analysis also got similar conclusion.[14] However, a body of recent studies provided inconsistent findings.[15–28] Therefore, we performed a meta-analysis to determine the predictive effect of HbA1c level on clinical outcomes in nondiabetic patients with CAD.

2. Methods

The present study was conducted according to MOOSE (Meta-analysis Of Observational Studies in Epidemiology) recommendations,[29] following a registered protocol on the PROSPERO database (CRD42016037303).

2.1. Data sources and search strategy

We comprehensively searched PubMed, EMBASE, MEDLINE, and the Cochrane Library from database inception to 10 April 2016 without restrictions of language and publication status. The following search terms were used: ("coronary artery disease" or "coronary heart disease" or "myocardial infarction" or "acute coronary syndrome" or "percutaneous coronary intervention") and ("glycated hemoglobin" or "hemoglobin A1c" or "HbA1c"). We also manually reviewed references of the identified articles and relevant reviews.

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2.2. Study selection

Two reviewers (GJ and YZ) independently assessed available studies. Any discrepancies were solved by discussion with a third author (BX). Studies with any study design were eligible if they compared the outcomes between high and low HbA1c levels in CAD patients without a history of DM. A threshold of 6.5% was preferred as the HbA1c cutoff because it is recommended as the diagnostic value for diabetes in recent guideline.[7] Also, all studies had to be followed up for at least 12 months and reported the outcomes for mortality or MI. We excluded abstracts and unpublished studies.

2.3. Data extraction

The primary endpoint was long-term mortality, and the second outcomes were early deaths and MI. Two reviewers (GJ and YZ) independently extracted studies characteristics and clinical and demographic information of enrolled patients in each study, and a third one (BX) verified. We extracted 30-day mortality as early deaths; for studies not reporting 30-day mortality, we used in-hospital mortality instead. We contacted the authors for any missing or unclear data.

2.4. Quality assessment

We assessed the quality of included studies using the Newcastle–Ottawa scale criteria, which includes 9 terms in 3 domains (selection, comparability, and outcome).[29] Studies with 8 or more terms were deemed to be of low risk of bias. Two reviewers (GJ and YZ) independently evaluated the quality, and a third one (BX) solved discrepancies.

2.5. Statistical analysis

Stata 12.0 was employed to analyze the pooled effects with odds ratios (ORs) and 95% confidence intervals (CIs). Heterogeneity was assessed using the χ^2-base Q test the I^2 test. A P value less than .10 or an I^2 more than 50% suggests significant heterogeneity.[30] We used the fixed effect model (Mantel–Haenszel method) for pooled analysis preferentially[31]; if high heterogeneity was indentified, we used the random effect model (DerSimonian and Larid method) instead.[32] Given considerable heterogeneity, we also performed sensitivity analyses by excluding 1 study at 1 time to evaluate the contribution of including studies for heterogeneity. Publication bias was estimated using Egger's test and funnel plot with the trim and fill method,[33,34] which was also utilized to adjust for publication bias from potential unpublished studies. For primary outcome, we also did subgroup analyses according to clinical status of enrolling patient, timing of HbA1c measurement, performing regions, the HbA1c cutoffs and percent of patients with newly diagnosed diabetes and undergoing percutaneous coronary intervention. Statistical significance was considered when a 2-tailed P value less than .05 was observed.

3. Results

Twenty studies comprising 22,428 nondiabetic patients with CAD from were included (Fig. 1).[8–13,15–28] All studies were published in English, except one in Spanish.[28] The mean age of enrolled patients across studies ranged from 51 to 70 years, and 71% of participants were men. All studies were of either retrospective or prospective cohort design, except 1 study, which
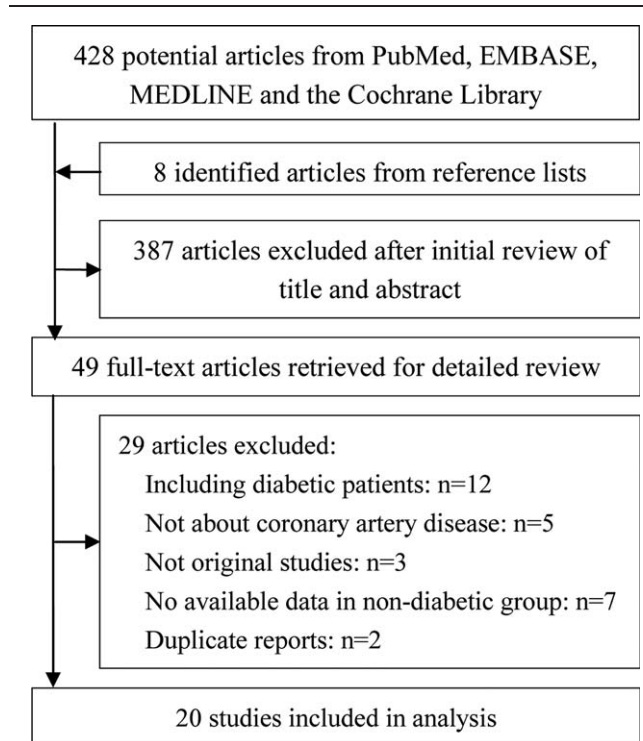

Figure 1. Flow diagram of the meta-analysis.

was a prespecified substudy of a randomized controlled trial.[12] Sixteen studies were conducted in patients with MI and 15 studies used the HbA1c level at admission to categorize the high and low HbA1c group in nondiabetic patients. The HbA1c cutoffs ranged from 5.1% to 6.0%. Patients with newly diagnosed DM were excluded in 14 studies. Detailed characteristics of eligible studies and nondiabetic patients with CAD are presented in Table 1 of Supplement 1, http://links.lww.com/MD/B678. Quality assessment of eligible studies according to the Newcastle–Ottawa scale criteria is available in Supplement 2, http://links.lww.com/MD/B679 (Table 1). Fourteen studies were considered to have low risk of bias.

3.1. Long-term mortality

A total of 14 studies provided long-term mortality data with a median follow-up of 2.5 years (range 1–7 years).[8–13,15,18,19,21–28] Three studies did not report mortality data based on HbA1c levels in the articles; but we obtained data of 2 studies from a prior meta-analysis,[9,11] and data of the other study by contacting the primary authors.[23] In total, 18,041 participants were included for the pooled analysis, which showed a significantly increased risk of long-term mortality in patients with a high HbA1c level than those with a low HbA1c level (OR 1.76, 95%CI 1.44–2.16, $P < .001$, Fig. 2). There were significant heterogeneity among these studies ($I^2 = 56.6\%$, $P = .002$). Subgroup analyses showed that these findings were independent from the clinical status of enrolling patients, the timing of HbA1c measurement, the HbA1c cutoffs, and the percent of patients having percutaneous coronary intervention. Also, whether newly diagnosed diabetes was included or not in the study did not affect the results (Table 1). However, it should be noted that the increased ratio was more remarkable when the HbA1c cutoff was higher (P for interaction < .01).

Table 1

Subgroup analyses of long-term mortality using a random effect model.

Subgroup	No. of studies	OR (95%CI)	I^2 (%)	P for interaction
Diagnosis				
STEMI	7	1.44 (1.09–1.91)	39	.31
Myocardial infarction	6	2.07 (1.40–3.04)	76	
Others	4	1.77 (1.33–2.36)	0	
Timing of HbA1c measured				
Admission	13	1.79 (1.35–2.37)	64	.94
Others	4	1.77 (1.45–2.15)	0	
Region				
North America	3	1.26 (0.85–1.86)	47	.11
Europe	9	2.03 (1.59–2.58)	50	
Others	5	1.55 (1.01–2.38)	34	
Threshold of HbA1c level				
>5.7%	7	3.06 (1.74–5.38)	66	<.01
=5.7%	6	1.31 (1.10–1.55)	0	
<5.7%	4	1.75 (1.41–2.18)	0	
Excluding newly diagnosed diabetes				
Yes	12	1.91 (1.39–2.64)	69	.60
No	5	1.73 (1.44–2.08)	0	
Percentage of undergoing PCI, %				
≥90%	9	1.84 (1.23–2.76)	73	.66
<90%	8	1.67 (1.42–1.97)	4	

CI = confidence interval, HbA1c = glycated hemoglobin, OR = odds ratio, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

Sensitivity analyses showed no alteration of the main outcome after elimination of each study. Specially, study heterogeneity was much less when the study by Kowalczyk was omitted (I^2 = 17.7%, P = .251), and the pooled estimate of OR was 1.56 (95% CI 1.36–1.80, P < .001).[24]

Egger's test was statistical significant (P = .037) and visual inspection of the funnel plot seemed to be asymmetric. The trim and fill method suggested there might be 6 unpublished studies (Fig. 1 of Supplement 2, http://links.lww.com/MD/B679). Using the trim and fill method, our finding of long-term mortality remained significant after adjustment for 6 unpublished studies (OR 1.51, 95% CI 1.20–1.91, P = .001).

Four studies also provided data adjusted for other confounding factors.[10,24,26,27] Pool analysis of these 4 study confirmed the conclusion that the elevated HbA1c level was associated with higher long-term mortality (OR 2.46, 95% CI 2.19–2.73, P < .001). A significant heterogeneity was noted (I^2 = 98.2%, P < .001).

3.2. Early deaths

Nine studies with 13609 patients contributed to the analysis of early death.[13,15–18,20,25–27] Meta-analysis did not find significant difference in rate of early deaths between patients with high HbA1c levels and those with low HbA1c levels (OR 1.08, 95% CI 0.92–1.27, P = .359), with no evidence of heterogeneity across the studies (I^2 = 0%, P = .494, Fig. 3). We found no change of pooled estimate effect and heterogeneity after sensitivity analyses. Egger's test revealed no statistical significant (P = .169); however, the funnel plot seemed to be asymmetric, indicating potential
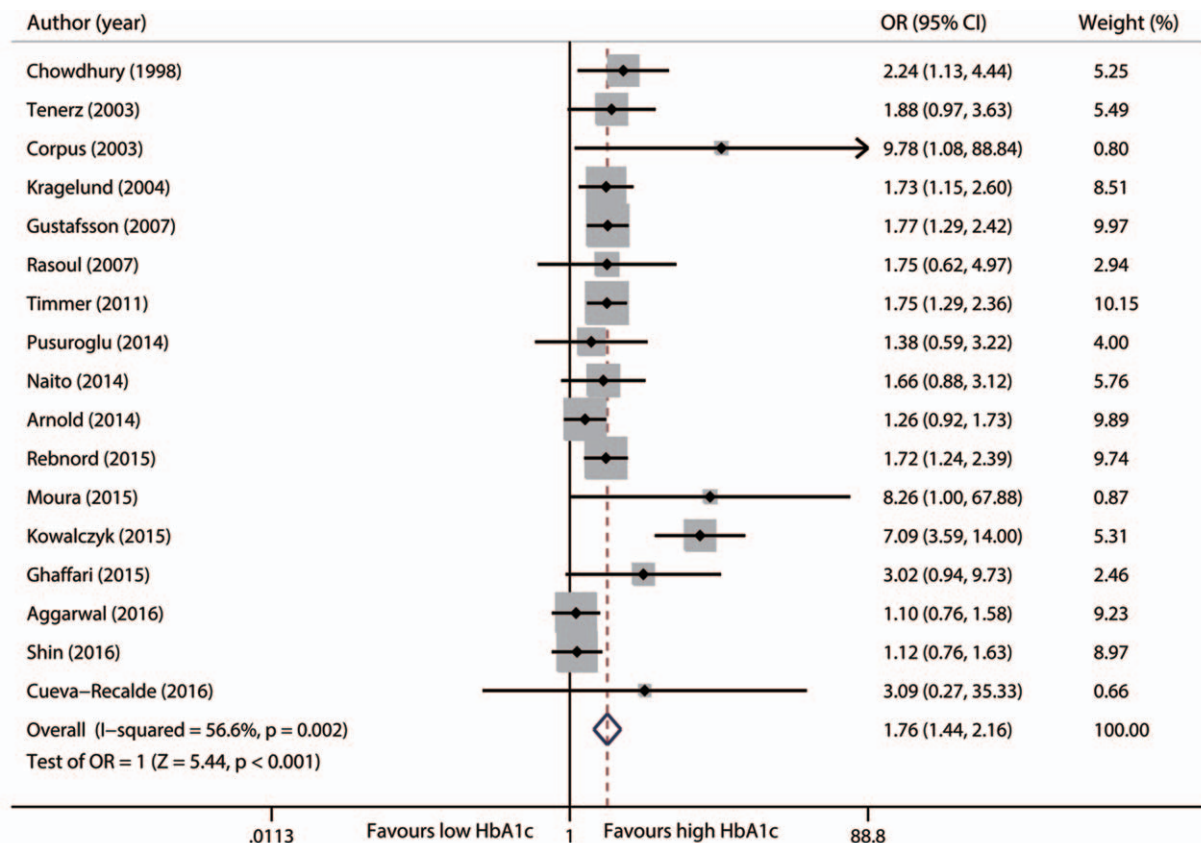

Author (year)	OR (95% CI)	Weight (%)
Chowdhury (1998)	2.24 (1.13, 4.44)	5.25
Tenerz (2003)	1.88 (0.97, 3.63)	5.49
Corpus (2003)	9.78 (1.08, 88.84)	0.80
Kragelund (2004)	1.73 (1.15, 2.60)	8.51
Gustafsson (2007)	1.77 (1.29, 2.42)	9.97
Rasoul (2007)	1.75 (0.62, 4.97)	2.94
Timmer (2011)	1.75 (1.29, 2.36)	10.15
Pusuroglu (2014)	1.38 (0.59, 3.22)	4.00
Naito (2014)	1.66 (0.88, 3.12)	5.76
Arnold (2014)	1.26 (0.92, 1.73)	9.89
Rebnord (2015)	1.72 (1.24, 2.39)	9.74
Moura (2015)	8.26 (1.00, 67.88)	0.87
Kowalczyk (2015)	7.09 (3.59, 14.00)	5.31
Ghaffari (2015)	3.02 (0.94, 9.73)	2.46
Aggarwal (2016)	1.10 (0.76, 1.58)	9.23
Shin (2016)	1.12 (0.76, 1.63)	8.97
Cueva–Recalde (2016)	3.09 (0.27, 35.33)	0.66
Overall (I-squared = 56.6%, p = 0.002)	1.76 (1.44, 2.16)	100.00
Test of OR = 1 (Z = 5.44, p < 0.001)		

.0113　　Favours low HbA1c　　1　　Favours high HbA1c　　88.8

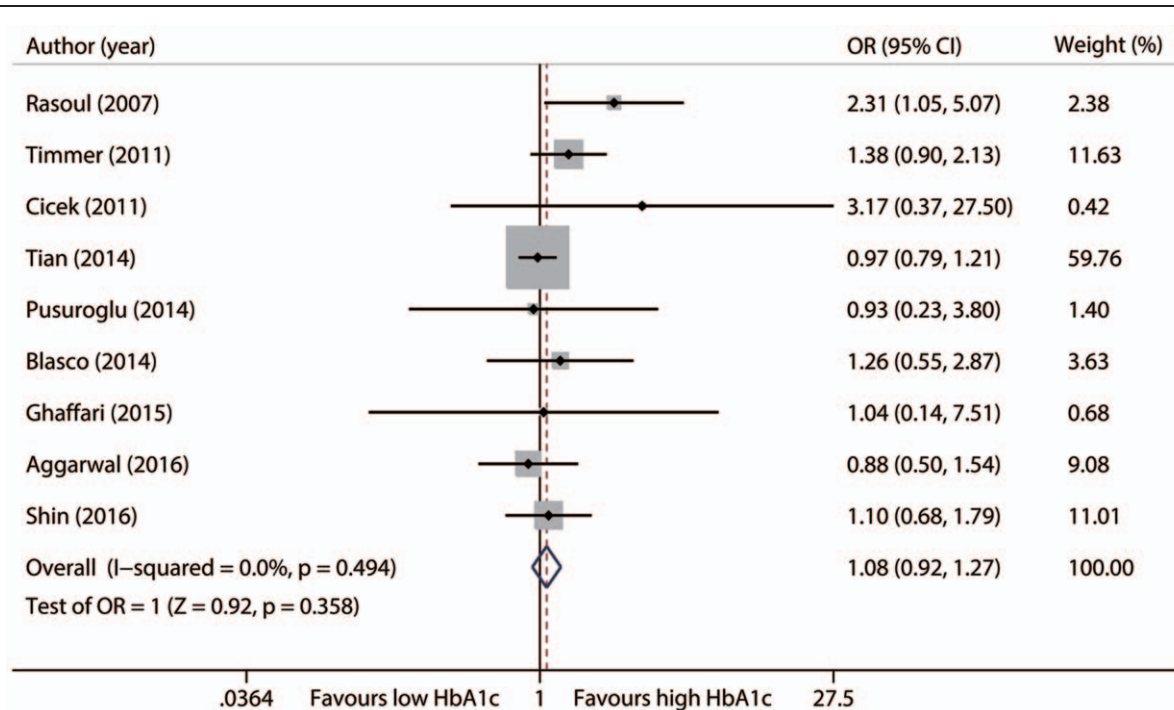**Figure 2.** Forest plot for long-term mortality.

Figure 3. Forest plot for early deaths.

publication bias. We found that there might be 2 unpublished studies with the trim and fill approach (Fig. 2 of Supplement 2, http://links.lww.com/MD/B679). The difference still remained nonsignificant after adding these 2 potential unpublished studies (OR 1.06, 95%CI% 0.86–1.32, $P=.567$).

3.3. Myocardial infarction

Five studies with 3664 nondiabetic patients reported data on MI.[18,19,23,27,28] High HbA1c levels were associated with a significantly higher risk of MI (OR 1.69, 95%CI 1.07–2.67, $P=.026$). No significant heterogeneity was found ($I^2=0\%$, $P=.407$, Fig. 4). The association disappeared after adjustment for potential publication bias by the trim and fill method (OR 1.57, 95%CI 0.99–2.48, $P=.053$) (Fig. 3 of Supplement 2, http://links.lww.com/MD/B679). This risk difference also became nonsignificant after either the study of Pusuroglu and colleagues (OR 1.51, 95%CI 0.88–2.57, $P=.133$) or the study of Moura and colleagues (OR 1.52, 95%CI 0.92–2.53, $P=.104$) was excluded.[18,23]
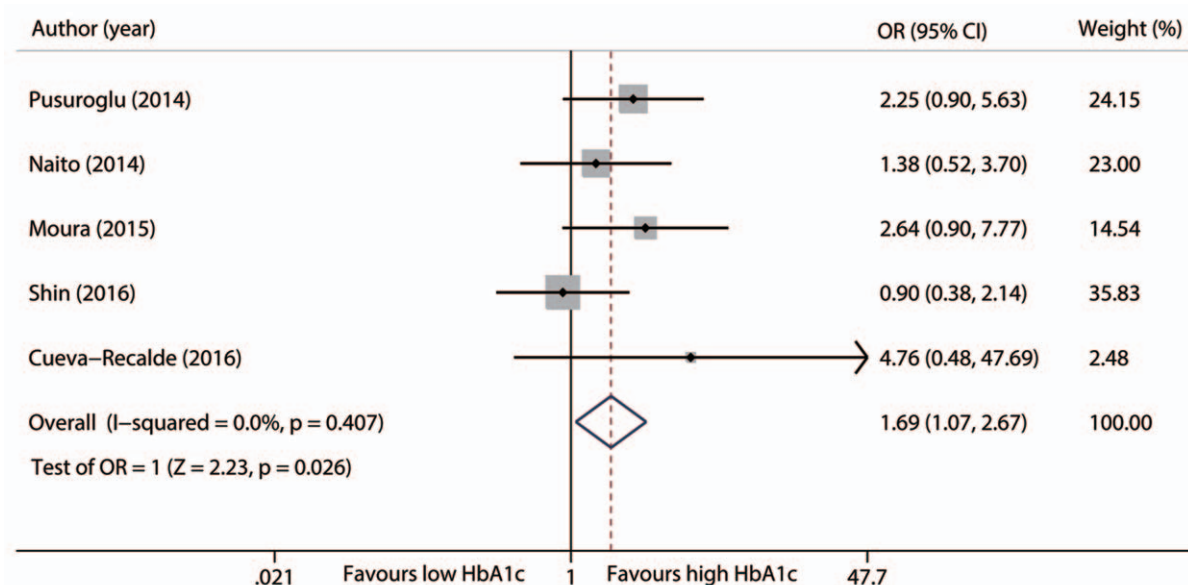

Figure 4. Forest plot for reinfarction during follow-up.

4. Discussion

This meta-analysis showed that the elevated HbA1c level was associated with long-term mortality, but not with early deaths in nondiabetic patients with CAD. These findings were further confirmed by sensitivity analyses and the trim and fill method. Moreover, patients with a high HbA1c level had a higher incidence of MI.

Our results were similar to a previous meta-analysis by Liu,[14] which also showed an increased mortality in nondiabetic patients with elevated HbA1c levels. However, this study differed in the following aspects. First, Liu included 7 studies comprising 5944 nondiabetic patients for the subgroup analysis of mortality,[14] while we added recent 14 studies including more than 20 thousands subjects. Second, we provided short- and long-term mortality data in nondiabetic population and also provided the data of MI by pooled analysis from 3664 nondiabetic patients. Third, the cut-off HbA1c levels to distinguish the high and low HbA1c levels included 7% and 7.5% in previous meta-analysis, suggesting that there were also diabetic individuals included in the subgroup analysis of nondiabetic population.

The association of increased blood glucose with short-term mortality has been well established.[1,2] The high blood glucose level is often observed in CAD patients with an acute event owing to stress response.[35] It is reported that 25% of AMI patients had newly diagnosed DM.[3] AMI patients with newly diagnosed DM had a nearly 2-fold risk of long-term mortality compared with nondiabetic ones.[26] However, using the glucose test, we may fail to identify the undiagnosed DM due to high prevalence of stress hyperglycemia in this population. HbA1c reflects long-term glycometabolic control,[6] and its level as higher than 6.5% is now considered as an alternative category of DM.[7] Our data provided the relationship between the HbA1c level and clinical outcomes, indicating that HbA1c might have a better prognostic value in nondabetic patients.

HbA1c had no predictive value for short-term outcomes based on our results. One possible explanation is that high HbA1c levels result from long-term insulin resistance, leading to dyslipidemia, hypercoagulability inflammation, and subsequent cardiovascular events.[36,37] Besides, nondiabetic individuals with high HbA1c levels have an increased risk of developing DM, which may need a long-term follow-up. CAD patients with DM, even the ones with newly diagnosed DM, have excess risk for developing adverse outcomes.[26] However, in a short-term follow-up, the ability to detect the difference in deaths may be limited by small numbers of incident DM. Moura et al[23] reported a high incidence of newly diagnosed DM in patients with high HbA1c levels, but found no association between newly diagnosed DM and outcomes. However, these results might be hampered by the small sample size. More studies are needed to evaluate the association of newly diagnosed DM with long-term mortality in larger sample size and longer follow-up.

According to a recent guideline for DM diagnosis, HbA1c from 5.7% to 6.5% is considered as prediabetes.[7] In the present meta-analysis, the threshold of HbA1c was 5.7% in 8 studies, and subgroup analysis by HbA1c levels showed that prediabetes was significantly associated with long-term mortality (OR 1.31, 95% CI 1.10–1.55). The prevalence of prediabetes and CAD are 15.5% and 1.76% in China respectively,[38,39] suggesting that there are approximately 4 million nondiabetic patients with CAD in China and will be much more across the world. More interventions, such as lifestyle change or pharmacological therapy, need to be assessed in this population to decrease the risk of adverse outcomes. Lifestyle intervention or metformin may reduce the incidence of DM in nondiabetic individuals[40] and may be beneficial for improving clinical outcomes in theory. Results from large-scale studies with high quality are critically needed to evaluate the effect of therapeutic options in nondiabetic patients with CAD.

There are several limitations presented in this meta-analysis. First, the pooled data were derived from observational studies and baseline characteristics of included patients differed in some confounders. We conducted the meta-analysis of adjusted mortality from 4 studies and got consistent result. Besides, sensitivity analysis and trim and fill method did not alter the results of our primary outcome, lessening the adverse effect from this limitation. However, for the secondary outcomes, no relevant data of adjusted results were obtained. Second, our results of long-term mortality had moderate heterogeneity. We found no significant heterogeneity after exclusion of Kowalczyk's study because Kowalczyk only enrolled patients with impaired glucose tolerance in the nondiabetic group.[24] Diverse regions of the patients in these studies may also explain part of the moderate heterogeneity according to our results of sub-group analyses. Third, there was significant publication bias for long-term mortality given the results of Egger's test and the funnel plot. For early deaths and MI, statistical analyses reached no significance, but potential publication bias still existed based on visual inspection of the funnel plot. We improved the credibility of results in long-term mortality and early deaths using sensitivity analysis and the trim and fill method. The result of MI, however, was still less conclusive. Finally, in-hospital and follow-up managements, such as intervention procedures and medications, may influence the clinical outcomes. We conducted subgroup analysis according to the percentage of percutaneous coronary intervention and found no alternation of the primary endpoint. Besides, we speculate that incident of DM may be partially contribute to the higher long-term mortality in nondiabetic patients with CAD. However, scant comparative data of medication and newly diagnosed diabetes are available for further analysis.

5. Conclusions

In conclusion, we found that the elevated HbA1c level is associated with long-term mortality and MI, but not with early deaths in nondiabetic patients with CAD. These findings may be partially attributed to newly diagnosed DM during follow-up. Future studies are required to confirm this assumption and identify whether lifestyle and pharmacological intervention can improve the long-term outcomes in this population.

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