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Letter to the Editor

Glycosylated hemoglobin levels and clinical outcomes in diabetic patients receiving percutaneous coronary interventions: A meta-analysis of cohort studies

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In recent years, percutaneous coronary interventions (PCI) have become a common therapy for patients with coronary artery disease (CAD). However, there is still high occurrence of major adverse cardiovascular events (MACEs) and stenosis after stent implantation, especially in diabetes mellitus (DM) patients [1–3]. Although several studies investigated the association between baseline glycosylated hemoglobin (HbA1c) level and clinical outcomes in diabetic patients following PCI [4–19], no consistent results were reported. We thus performed a meta-analysis of cohort studies to evaluate whether HbA1c level was independently associated with the outcomes in DM patients undergoing PCI.

We performed a comprehensive literature search in Pubmed, Embase, and Web of Science for studies assessing the association between HbA1c levels and clinical outcomes in diabetic patients receiving PCI. The search time was from their commencements to December 16, 2014, and there was no language restriction. We used the following search terms: (hemoglobin a1c OR hemoglobin A1c OR A1c OR HbA1c OR glycosylated hemoglobin) AND (stenting OR stent OR coronary stent OR coronary angioplasty OR coronary intervention OR revascularization OR coronary stenting OR stent implantation). Hand checking of references of relevant reviews or eligible studies was also carried out to identify other possible studies. The inclusion criteria in the meta-analysis were as following: (1) Prospective or retrospective cohort studies; (2) the outcomes of interests were MACEs, target vessel revascularization (TVR), all-cause mortality, and restenosis; (3) estimated the impact of HbA1c levels on risks of MACEs, TVR, all-cause mortality, or restenosis; (4) reported risk estimates, such as relative risks (RR), hazard ratios (HR), or odds ratios (OR) with 95% confidence intervals (95% CI), or other data to calculate the risk estimates. When multiple reports from the same cohort study were reviewed, the article with the longest follow-up for identical outcomes was included.

The main outcome of interest was MACEs, and the second outcomes of interest were TVR, all-cause mortality, and restenosis. Two members of the review team extracted data, and disagreements were settled by discussion among all investigators. For each study, the following data were extracted: first author's last name, publication year, study design, sample size, country, baseline characteristics, length of follow-up, cut-off value of HbA1c, variables adjusted for in the multivariate statistical analysis, types of outcomes, definition of outcomes, risk estimate (RR, HR, or OR) with 95% CI. This study collected data for maximally adjusted risk estimates. The quality of included studies was assessed using the Newcastle Ottawa Scale (NOS) [20]. This scale awards a maximum of nine stars to each study: four stars for the adequate selection of cohort participants, two stars for comparability of cohort participants on the basis of the design and analysis, and three stars for the adequate ascertainment of outcomes. Quality was assigned as high quality with 6–9 stars, and suboptimal quality with 0–5 stars.

The study abstracted risk estimates with 95% CI for the association between HbA1c levels and clinical outcomes in diabetic patients receiving PCI. The random-effects model (DerSimonian and Laird method) to calculate the pooled RR and 95% CI was used [21]. When there was no obvious heterogeneity among those included studies, the fixed-effects model was used. Heterogeneity was assessed using Cochran's $\chi 2$ method and the I2 statistic [22]. When P values for Cochran's test was less than 0.05 or the I2 was more than 50%, there was obvious heterogeneity among those included studies. Potential publication bias was assessed by visual inspection of the funnel plot, and an asymmetric plot suggested possible publication bias. In addition, this study also performed Egger linear regression test at the $P < 0.05$ level of significance to assess the funnel-plot's asymmetry. Statistical analyses were performed using Stata 12.0 (StataCorp, College Station, Texas, USA). P values < 0.05 were considered statistically significant.

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Table 1
Characteristics of those 16 included cohort studies in the meta-analysis.

Study	Study design	Gender	Country	Total participants	Follow-up	HbA1c definition	Type of outcomes	Adjustment	NOS
Hong LF 2014 [4]	Prospective	Mixed	China	328 patients	12 months	H vs L	MACEs (cardiac death, MI, revascularization, re-hospitalization for acute coronary syndrome)	Yes	8
Ike A 2014 [5]	Retrospective	Mixed	Japan	758 patients	300 days	H vs L	MACEs (deaths, MI, TLR)	Yes	8
Kassaian SE 2012 [6]	Prospective	Mixed	Iran	703 patients	12 months	>7%	MACEs (TVR, non-fatal MI, cardiac death)	No	5
Singla A 2012 [7]	Prospective	Mixed	USA	231 patients	365 days	>8.8%	MACEs (death, MI ,stent thrombosis, TVR)	No	5
Sawai T 2012 [8]	Retrospective	Mixed	Japan	415 patients	7 months	>7%	MACEs (cardiac death, MI, TLR, CABG)	No	5
Ueda H 2010 [9]	Retrospective	Mixed	Japan	206 patients	23 months	H vs L	MACEs (death, MI, congestive heart failure, TLR)	Yes	8
Ehara N 2010 [10]	Retrospective	Mixed	Japan	1504 patients	1278 days	>8%	MACEs (cardiovascular death, MI, stroke)	No	5
Lemesle G 2009 [11]	Retrospective	Mixed	USA	952 patients	1 year	>7%	MACEs (death, MI, TVR)	Yes	8
Kereiakes DJ 2008 [12]	Prospective	Mixed	USA	431 patients	8 months	H vs L	MACEs (cardiac death, TVR, MI)	No	5
Sharma 2014 [13]	Retrospective	Mixed	USA	3008 patients	5.4 years	>10.0%	All-cause mortality	Yes	8
Lazzeri C 2014 [14]	Retrospective	Mixed	Italy	276 patients	1 year	H vs L	All-cause mortality	Yes	8
Kasai T 2007 [15]	Retrospective	Mixed	Japan	298 patients	12.0 years	H vs L	All-cause mortality	Yes	8
Lindsay J 2006 [16]	Retrospective	Mixed	USA	142 patients	9 months	>7%	TVR	No	5
Corpus R.A. 2004 [17]	Prospective	Mixed	USA	179 patients	12 months	H vs L	TVR	No	5
Park HJ 2010 [18]	Prospective	Mixed	Korea	35 patients	6–9 months	>7%	Restenosis	No	5
Mazeika P 2003 [19]	Prospective	Mixed	Canada	75 patients	6 months	>8%	Restenosis	Yes	8

Sixteen cohort studies finally met the inclusion criteria and were included into the meta-analysis. Those 16 cohort studies included a total of 9541 diabetic participants receiving percutaneous coronary interventions. Table 1 showed the main characteristics of those 16 included cohort studies in the meta-analysis (Table 1). Among those 16 studies, 9 studies assessed the impact of HbA1c level on incidence of MACEs, 2 studies assessed the impact of HbA1c level on incidence of TVR, 2 studies assessed the impact of HbA1c level on incidence of restenosis, and 3 studies assessed the impact of HbA1c level on incidence of all-cause-mortality. The duration of follow-up varied from 6 months to 12 years. 8 studies were from Asia, and 7 studies were from North America, and one study was from Europe (Table 1). According to the NOS criteria, 8 studies had high quality, while the other 8 studies had suboptimal quality (Table 1).

Meta-analysis of total 16 studies showed that high HbA1c was associated with increased risk of MACEs with RR of 1.18 (95% CI 1.10–1.27, P = 0.016; I^2 = 45.8%) (Fig. 1). Meta-analysis of 8 studies with high quality also showed that high HbA1c was significantly and independently associated with increased risk of MACEs (adjusted RR = 1.21, 95% CI 1.03–1.43, P = 0.005; I^2 = 65.9%) (Fig. 2).

Subgroup analyses were further performed by types of MACEs. Meta-analysis of 9 studies using MACEs as outcome showed that high HbA1c was significantly associated with increased risk of MACEs (RR = 1.13, 95% CI 1.03–1.23 P = 0.006; I^2 = 45.8%) (Fig. 3). Meta-analysis of 5 studies using mortality as outcome showed that high HbA1c was not significantly associated with risk of mortality (RR = 1.10, 95% CI 0.77–1.58, P = 0.599; I^2 = 69.0%). Meta-analysis of 3 studies using MI as outcome showed that high HbA1c was not significantly associated with risk of MI (RR = 1.31, 95% CI 0.78–2.19, P = 0.309; I^2 = 0%). Similarly, meta-analysis of 5 studies on TVR showed that high HbA1c was not significantly associated with increased incidence of TVR (RR = 1.20, 95% CI 0.91–1.58, P = 0.186, I^2 = 40.9%).

Funnel plot's shape did not reveal obvious evidence of asymmetry. In addition, the P value of Egger's test in the meta-analysis of total 16

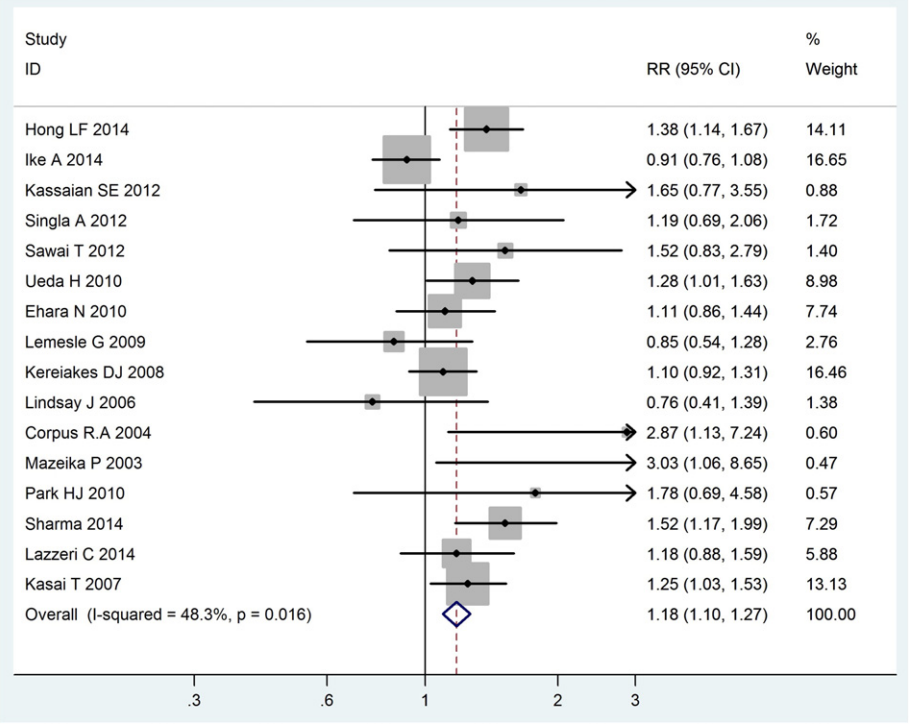

Fig. 1. High HbA1c level was associated with increased risk of MACEs in the meta-analysis of total 16 studies.