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Title	Association of Hemoglobin A1c Levels With Cardiovascular Disease and Mortality in Chinese Patients With Diabetes
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Letters

Association of Hemoglobin A1c Levels With Cardiovascular Disease and Mortality in Chinese Patients With Diabetes

Among diabetic patients, hemoglobin A1c (HbA1c) is an important indicator of glycemic control and, together with blood pressure and cholesterol, is an indicator for risk of complications, including cardiovascular disease (CVD) and mortality. At present, there is no universal consensus on the optimal HbA1c level. Despite this, most international guidelines include a recommended HbA1c target range or level as a treatment goal. Several studies have identified a J-shaped curvilinear relationship between HbA1c and CVD incidence and all-cause mortality, but such a relationship has not yet been confirmed in a Chinese population (1). There are substantial differences in disease risks across racial and ethnic groups due to genetic and environmental factors including life-style and health behaviors, and thus, previous results from Western studies may not be transferable to a Chinese population (2). We sought to examine the association among mean HbA1c, CVD events, and mortality among Chinese primary care patients with type 2 diabetes mellitus (T2DM) in Hong Kong.
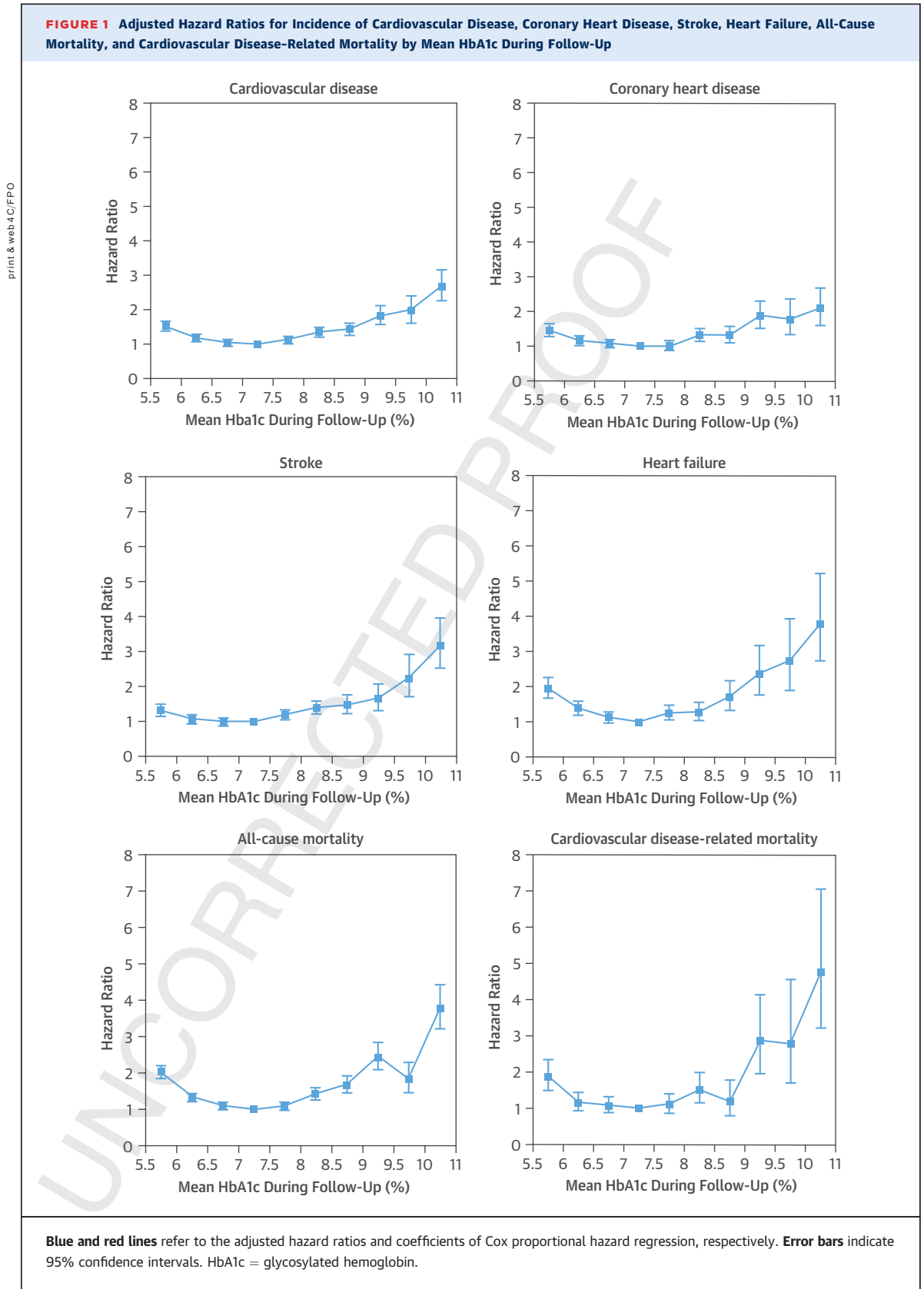
A population-based retrospective cohort study was conducted on 117,389 Chinese adult T2DM primary care patients without any CVD history and who had an HbA1c value recorded between August 1, 2008, and December 31, 2009. Data was extracted from the computerized administrative database of Hong Kong Hospital Authority. The date of the first recorded HbA1c was used as the baseline date for each subject. Each subject was then tracked to identify: the date of incidence of an outcome event, the date of all-cause mortality, or until December 31, 2013, whichever came first. The study outcomes included: 1) CVD event with 1 of the following subtype diagnoses: coronary heart disease (CHD), stroke, or heart failure; 2) CHD; 3) stroke; 4) heart failure;

5) all-cause mortality; and 6) CVD-related mortality. Comorbidities were identified by the diagnosis coding system of International Classification of Primary Care-2 and International Classification of Diseases, Ninth Edition, Clinical Modification. A "mean HbA1c" value was determined by calculating the average of all HbA1c measurements collected during follow-up. Baseline covariates included: age; sex; smoking status; drinking habit; body mass index; waist-to-hip ratio; systolic and diastolic blood pressure; low-density lipoprotein cholesterol; total cholesterol to high-density lipoprotein cholesterol ratio; triglycerides; urine albumin-to-creatinine ratio; self-reported duration of diabetes; family history of diabetes; hypertension; the stage of chronic kidney disease; and baseline use of antihypertensive drugs, metformin, sulfonylurea, other oral antidiabetic drugs (acarbose, glitazone, gliptin, glucagon-like peptide-1 agonist, and meglitinides), insulin, and lipid-lowering agents.

Missing data (other than HbA1c) were handled by multiple imputation method. Study subjects were divided into 10 groups according to their mean HbA1c measurement ($<6.0\%$, $\geq6.0\%$ to $<6.5\%$, $\geq6.5\%$ to $<7.0\%$, $\geq7.0\%$ to $<7.5\%$, $\geq7.5\%$ to $<8.0\%$, $\geq8.0\%$ to $<8.5\%$, $\geq8.5\%$ to $<9.0\%$, $\geq9.0\%$ to $<9.5\%$, $\geq9.5\%$ to $<10.0\%$, and $\geq10.0\%$). The relationship between HbA1c group and study outcomes were evaluated using multivariable Cox Proportional Hazard regression, adjusting for all baseline covariates. The statistical procedures were repeated using updated HbA1c as a time-updated analysis.

After a median follow-up of 54.5 to 58.5 months, amongst the 10 HbA1c groups, unadjusted incidence rates for CVD events and all-cause mortality were 13.8 to 28.8 and 9.4 to 32.3 per 1,000 person-years, respectively. A J-shaped curvilinear relationship was identified between HbA1c levels and CVD incidence, all-cause mortality, as well as other outcomes (**Figure 1**). An HbA1c range of $\geq7.0\%$ to $<7.5\%$ had the lowest risk of new CVD, CHD, stroke, heart failure, all-cause mortality, and CVD-related mortality. When compared to a HbA1c range of $\geq7.0\%$ to $<7.5\%$, HbA1c $<6.5\%$ or $\geq8.0\%$ was associated with a significantly higher incidence of CVD and all-cause mortality. Similar results were obtained in the time-updated analysis.

FIGURE 1 Adjusted Hazard Ratios for Incidence of Cardiovascular Disease, Coronary Heart Disease, Stroke, Heart Failure, All-Cause Mortality, and Cardiovascular Disease-Related Mortality by Mean HbA1c During Follow-Up

Blue and red lines refer to the adjusted hazard ratios and coefficients of Cox proportional hazard regression, respectively. **Error bars** indicate 95% confidence intervals. HbA1c = glycosylated hemoglobin.

This study had several limitations. This was a retrospective cohort study, which is lower in terms of evidence hierarchy than a randomized controlled trial. Drug exposure over time and lifestyle behavior risk factors such as diet and exercise were not taken into account in the analyses. This study was undertaken in Hong Kong, and the pattern of association between HbA1c and outcomes may differ in other Chinese populations. The relationship may be subject to temporal changes and modifications in unmeasured risk factors or interventions.

The results of this territory-wide, naturalistic, cohort study of Chinese primary care patients with T2DM supports the findings of previous observational studies conducted in the United States, United Kingdom, Denmark, and Netherlands, demonstrating a J-shaped pattern of association between HbA1c and CVD and all-cause mortality (1). Similar J-shaped relationships were also identified for CHD, stroke, heart failure, and CVD-related mortality. Although this phenomenon has been postulated to be related to the deleterious effects of severe hypoglycemia (3), this is controversial, and it remains unclear why low levels of HbA1c are associated with a higher risk of CVD and all-cause mortality.

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