Hyperglycemia and Mortality Among Patients With Coronary Artery Disease

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OBJECTIVE

Known diabetes is an independent predictor for mortality in coronary artery disease (CAD) patients; however, whether other glucose abnormalities are associated with death risk in CAD patients is unclear. The goal of this study was to examine the association between different glucose states and the risks of all-cause and cardiovascular disease (CVD) mortality among CAD patients.

RESEARCH DESIGN AND METHODS

The study cohort included 1,726 CAD patients who were 40–85 years of age in the Guangdong Coronary Artery Disease Cohort. Cox proportional hazards regression models were used to estimate the association of baseline glucose status with risk of mortality.

RESULTS

During a median follow-up of 3.1 years, 129 deaths were recorded, 109 of which were due to CVD. The multivariable-adjusted (age; sex; education; marriage; leisure-time physical activity; smoking; alcohol drinking; BMI; systolic blood pressure; total and HDL cholesterol; glomerular filtration rate; type, severity, duration, and treatment of CAD; history of heart failure; and use of antihypertensive, cholesterol-lowering, and antiplatelet drugs) hazard ratios in normoglycemia, impaired glucose regulation (IGR), newly diagnosed diabetes, and known diabetes were 1.00, 1.58 (95% CI 0.90–2.77), 2.41 (1.42–4.11), and 2.29 (1.36–3.84) for all-cause mortality and 1.00, 1.89 (1.01–3.54), 2.74 (1.50–5.01), and 2.73 (1.52–4.91) for CVD mortality. Assessing fasting plasma glucose only, impaired fasting glucose and newly diagnosed and known diabetes were also associated with increased risks of all-cause and CVD mortality compared with normoglycemia.

CONCLUSIONS

CAD patients with IGR, newly diagnosed diabetes, and known diabetes have increased risk of CVD mortality.

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Diabetes is one of the major public health burdens in the world and serves as a well-established risk factor for coronary artery disease (CAD). According to the International Diabetes Federation, >371 million people (8.3% of the population) have diabetes worldwide, and half of them are undiagnosed (1). The situation in China is more severe. With rapid economic development and lifestyle changes that come along, the prevalence of diabetes increases to 9.7% of Chinese adults, and the undiagnosed rate is up to 60%, which far exceeds the average worldwide level (2).

As a primary contributor to CAD, diabetes affects ~50% of CAD patients, and another 25% of CAD patients endure impaired glucose regulation (IGR) (3,4). It is well known that people with diabetes have a significantly increased premature mortality compared with nondiabetics, as well as two to four times the risk of developing cardiovascular disease (CVD), which is presently the leading cause of death both in China and worldwide (5–8). However, whether people with undiagnosed diabetes or a prediabetes status have higher risks for CVD and premature death has not been fully established. Some studies showed no association; on the other hand, some studies showed a positive association that disappeared after adjustment for covariates (9–12). With regard to the secondary CVD risk, the studies are few and inconsistent (13,14). Moreover, none of the existing cohorts are based on Chinese or Asian CAD populations. Previous evidence has shown that Western CAD patients generally have worse CVD risk profiles than Chinese patients, which include a higher prevalence of hypertension, dyslipidemia, obesity, and alcohol use (13). However, Chinese CAD patient total and CVD mortality is as high as in Westerners. Thus, it is meaningful to focus on hyperglycemia and its relationship to the secondary risk of Chinese CAD patients. The aim of this study was to evaluate the association of different glucose states with the risks of all-cause and CVD mortality among Chinese CAD patients.

RESEARCH DESIGN AND METHODS

Participants

The recruitment of the Guangdong Coronary Artery Disease Cohort took place between October 2008 and December 2011 (15–17). We enrolled 1,984 successive patients who were admitted to the Cardiology Department of three superior specialty hospitals in Guangdong and diagnosed as CAD (ICD-10 codes I20–I25) according to World Health Organization 1999/2000 guidelines (18,19). After excluding 204 participants that were out of touch after baseline survey and 54 participants because of missing data, the final sample comprised 1,726 CAD patients aged 40–85 years (Supplementary Fig. 1). Compared with the retained participants, those excluded from the present analysis were generally younger (61.1 vs. 64.0 years). No differences in the percentage of males (61.9 vs. 66.1%) and BMI (23.8 vs. 23.9) were found. The study was approved by the Sun Yat-sen University ethnic committee, and all participants signed the informed consent.

Clinical Measurements

A standardized questionnaire on general information of examination date, birth date, sex, education level, leisure-time physical activity, smoking habits, alcohol consumption, family history of CAD, and medication history and a validated food frequency questionnaire (20) were conducted through a face-to-face interview. Smoking was defined as at least one cigarette per day and lasting more than half a year. Alcohol drinking was defined as drinking any type of alcoholic beverage at least once a week and lasting >6 months. Smoking and drinking status were classified as never, past, or current (21).

Clinical characteristics, clinical test results, and treatment of participants were collected from an electronic case record system. At admission, trained nurses measured height, weight, and blood pressure using a standard protocol (22). BMI was calculated by dividing weight in kilograms by the square of height in meters. A venous blood specimen was drawn in the next morning after hospital admission with at least 12 h fasting. Lipids and fasting plasma glucose (FPG) were determined by standard methods. Glomerular filtration rate (GFR) was used to assess renal function, which was estimated with the most recent Modification of Diet in Renal Disease (MDRD) Study equation for standardized serum creatinine (23): estimated GFR (eGFR) = $175 \times (\text{standardized serum creatinine in mg/dL})^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female). Severity of CAD was based on coronary artery stenosis degree of coronary angiography reports, which were categorized as not conduct, <50%, 50–74.9%, and ≥75%. Treatment information of CAD included percutaneous coronary intervention and coronary artery bypass graft. Patients without known or newly diagnosed diabetes (n = 1,054) were asked to have a standard 2-h oral glucose tolerance test (OGTT) when they were in a stable condition. An OGTT was measured in 643 patients. The results of the OGTT, or FPG only when OGTT was not conducted, were used to categorize patients.

Glucose States

According to the 2005 American Diabetes Association (ADA) recommendations for the diagnosis of diabetes (24), subjects were classified into four groups: known diabetes, newly diagnosed diabetes (FPG ≥7.0 mmol/L and/or 2-h glucose ≥11.1 mmol/L), IGR (FPG 5.6–6.9 mmol/L [impaired fasting glucose, IFG] and/or 2-h glucose 7.8–11.0 mmol/L [impaired glucose tolerance, IGT]), and normoglycemia (FPG <5.6 mmol/L and 2-h glucose <7.8 mmol/L). In addition, subjects were also classified into four groups based on FPG only: known diabetes, newly diagnosed diabetes (FPG ≥7.0 mmol/L), IFG (FPG 5.6–6.9 mmol/L), and normoglycemia (FPG <5.6 mmol/L).

Prospective Follow-up

Follow-up data were collected from hospital medical records of readmission, telephone contacts with patients or family members, and death registration at the Guangdong Provincial Center for Disease Control and Prevention. The surveys were followed to the end of July 2013 or patient death, whichever occurred first. The ICD codes were used to code the cause of death, and the ICD

codes I00–I99 were classified as CVD deaths.

Statistical Analysis

Differences in risk factors by different glucose states were analyzed by the general linear model after adjustment for age and sex. The associations between baseline glucose status (normoglycemia, IGR/IFG, newly diagnosed diabetes, and known diabetes) and the risks of all-cause and CVD mortality were analyzed by using Cox proportional hazards models. The proportional hazards assumption in the Cox model was assessed with graphical methods and with models including time-by-covariate interactions (25). In general, all proportionality assumptions were appropriate. All analyses were adjusted for age and sex, and further for education, marriage, smoking, alcohol drinking, leisure-time physical activity, BMI, systolic blood pressure (SBP), total cholesterol, HDL cholesterol, eGFR, types of CAD (acute and chronic), severity of CAD, duration of CAD, treatment of CAD, history of heart failure, and use of antihypertensive, cholesterol-lowering, and antiplatelet drugs. For patients without known diabetes, the receiver operator characteristic (ROC) curve analysis was used to evaluate predictive accuracy of continuous FPG and 2-h glucose level, and the spline plot was used to display continuous associations of FPG with all-cause and CVD mortality. Statistical significance was considered to be $P < 0.05$. All statistical analyses were performed with PASW for Windows, version 20.0 (IBM SPSS Inc., Chicago, IL) and SAS for Windows, version 9.3 (SAS Institute, Cary, NC).

RESULTS

Baseline characteristics according to glucose states were presented in Table 1. Patients with normoglycemia, IGR, newly diagnosed diabetes, and known diabetes constituted 31.1, 23.3, 21.2, and 24.4% of whole subjects.

During a median follow-up of 3.1 years, 129 deaths were recorded, 109 of which were due to CVD. The 20 non-CVD deaths consisted of 14 deaths from cancer and 6 deaths from asphyxia due to lung disease. Since the interactions between sex and glucose status on the risks of all-cause and CVD mortality were not statistically significant, data for men and women were combined in the analyses to maximize the statistical power. After adjustment for all confounding factors (age, sex, education, marriage, smoking, alcohol drinking, leisure-time physical activity, BMI, SBP, total cholesterol, HDL cholesterol, eGFR, types of CAD, severity of CAD, duration of CAD, treatment of CAD, history of heart failure, and use of antihypertensive, cholesterol-lowering, and antiplatelet drugs), CAD patients with known diabetes had a 2.29-fold risk of all-cause mortality (95% CI 1.36–3.84) and a 2.73-fold risk of CVD mortality (1.52–4.91), CAD patients with newly diagnosed diabetes had a 2.41-fold risk of all-cause mortality (1.42–4.11) and a 2.74-fold risk of CVD mortality (1.50–5.01), CAD patients with IGR had a 1.58-fold risk of all-cause mortality (0.90–2.77) and a 1.89-fold risk of CVD mortality (1.01–3.54), compared with normoglycemic subjects (Table 2 and Fig. 1).

Since FPG was more useful for clinical practice, we performed analyses on FPG classification only. The multivariable-adjusted hazard ratios (HRs) in normoglycemia, IFG, newly diagnosed diabetes, and known diabetes were 1.00, 1.80 (95% CI 1.09–2.98), 2.15 (1.26–3.66), and 2.09 (1.31–3.33) for all-cause mortality and 1.00, 1.99 (1.14–3.49), 2.48 (1.38–4.48), and 2.42 (1.44–4.06) for CVD mortality, respectively (Table 2). Considering the effect of antidiabetic drugs on the known diabetes patients, we further included this variable in the last multivariable-adjusted model. Based on FPG and OGTT, CAD patients with known diabetes had a 2.12-fold risk of all-cause mortality (1.09–4.14) and a 2.35-fold risk of CVD mortality (1.12–4.95); based on FPG only, CAD patients with known diabetes had a 1.93-fold risk of all-cause mortality (1.02–3.62) and a 2.07-fold risk of CVD mortality (1.04–4.13). CAD patients with known diabetes still had a significantly higher risk for all-cause and CVD mortality than those with normoglycemia despite the effect of antidiabetic drugs.

Owing to part of the sample taking OGTT tests, our glucose classification of CAD patients might be challenged. Thus, we further conducted analyses based on subjects with both 2-h glucose and FPG measurements (n = 1,118). CAD patients with known or newly diagnosed diabetes were still associated with increased risks of all-cause and CVD mortality compared with normoglycemic subjects (Table 3).

In the multivariable subpopulation analyses, the association between glucose status and mortality remained similar when participants were stratified by age, sex, BMI, and type of CAD (Supplementary Table 1). There were no significant interactions between glucose status and these variables with the risks of all-cause and CVD mortality except for BMI regarding CVD mortality.

In order to assess the association of continuous FPG level and OGTT results with the risk of mortality, ROC curves and spline plots were used to evaluate the two measurements. ROC curves showed that the area under the curve of FPG and OGTT was >0.60, whereas the area under the curve of OGTT with regard to CVD mortality was not significant due to the small sample size (Supplementary Table 2). Spline plots displayed a J-shaped association between continuous FPG level and mortality among CAD patients without known diabetes (Supplementary Fig. 2). The associations of FPG with the risks of all-cause and CVD mortality were nonlinear (P = 0.007 for all-cause mortality and P = 0.008 for CVD mortality in the linear association test; P = 0.17 for all-cause mortality and P = 0.38 for CVD mortality in the nonlinear association test). The lowest HRs of all-cause and CVD mortality were in patients with an FPG ~5 mmol/L. The risk increased below and above this FPG level, with the highest risks in the upper range of the FPG distribution. Analysis for 2-h glucose was not shown due to the small sample size and incident death numbers of patients with OGTT.

CONCLUSIONS

The current study found that Chinese CAD patients with IFG, newly diagnosed diabetes, and known diabetes were associated with increased risks of all-cause and CVD mortality compared with Chinese CAD patients with

Table 1—Baseline characteristics according to glucose states among CAD patients

Characteristic	Normoglycemia	IGR	Newly diagnosed diabetes	Known diabetes	*P* for difference
No. of participants (%)	537 (31.1)	402 (23.3)	366 (21.2)	421 (24.4)	
Male (%)	66.5	71.4	68.3	59.1	0.002
Age (years)	63.9 (0.5)	63.1 (0.6)	63.0 (0.6)	65.8 (0.5)	0.001
FPG (mmol/L)	4.88 (0.10)	5.80 (0.12)	7.72 (0.12)	8.22 (0.12)	<0.001
2-h glucose (mmol/L)	6.32 (0.26)	8.79 (0.20)	12.07 (0.18)	—	<0.001
BMI (kg/m^2)	23.6 (0.1)	23.8 (0.2)	24.1 (0.2)	24.3 (0.2)	0.003
SBP (mmHg)	133 (1.0)	134 (1.2)	133 (1.2)	137 (1.2)	0.03
Diastolic blood pressure (mmHg)	77 (0.6)	77 (0.7)	77 (0.7)	78 (0.7)	0.70
Total cholesterol (mmol/L)	4.67 (0.05)	4.68 (0.05)	4.86 (0.06)	4.63 (0.05)	0.02
Triglycerides (mmol/L)	1.74 (0.06)	1.74 (0.07)	2.01 (0.07)	1.98 (0.07)	0.002
LDL cholesterol (mmol/L)	2.94 (0.04)	2.98 (0.05)	3.12 (0.05)	2.93 (0.05)	0.02
HDL cholesterol (mmol/L)	1.11 (0.01)	1.08 (0.01)	1.06 (0.01)	1.04 (0.01)	0.001
Duration of CAD (years)					
First diagnosed CAD (*n* = 930)	—	—	—	—	
History of CAD (*n* = 796)	3.00 (1.00–7.57)	2.11 (0.55–1.90)	2.43 (0.82–9.20)	4.00 (1.08–9.64)	0.23
eGFR (mL/min/1.73 m^2), (%)					<0.001
≥90	24.3	33.0	30.2	27.2	
60–89	54.7	46.3	50.6	41.4	
30–59	20.1	18.2	17.3	26.0	
15–29	0.4	2.0	2.0	3.7	
<15	0.6	0.5	0.0	1.7	
Married (%)	91.0	94.7	91.3	89.1	0.16
Years of education (%)					0.81
≤9	59.8	59.7	62.4	63.5	
10–12	22.3	21.2	19.2	17.4	
≥13	17.9	19.1	18.5	19.1	
Smoking (%)					0.001
Never	60.7	57.0	54.8	67.7	
Past	8.2	10.8	9.1	10.1	
Current	31.1	32.2	36.1	22.2	
Alcohol drinking (%)					0.009
Never	80.3	73.3	75.5	80.2	
Past	5.5	10.9	5.4	7.7	
Current	14.3	15.8	19.1	12.1	
Leisure-time physical activity (%)					0.07
None	35.5	36.4	40.7	29.8	
<30 min/day	24.0	18.4	18.9	21.4	
≥30 min/day	40.5	45.2	40.4	48.8	
Family history of diabetes (%)	24.1	24.1	23.6	23.6	1.00
Type of CAD (%)					<0.001
Acute coronary syndrome	50.8	61.9	66.9	61.0	
Chronic CAD	49.2	39.1	33.1	39.0	
Coronary artery stenosis degree of coronary angiography					<0.001
Not conduct	36.3	32.2	24.2	35.9	
<50%	17.0	11.1	10.6	5.1	
50–74.9%	11.0	7.6	6.0	7.1	
≥75%	35.7	49.2	59.2	51.9	
History of diseases (%)					
CAD	50.0	43.5	36.9	51.6	<0.001
Hypertension	56.8	52.6	53.0	70.2	<0.001
Dyslipidemia	28.5	29.2	26.6	34.4	0.09
Heart failure	37.2	41.8	50.8	46.6	<0.001
Use of medication before admission (%)					
Antidiabetic drugs	—	—	—	68.6	
Insulin	—	—	—	15.0	

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Table 1—Continued

Characteristic	Normoglycemia	IGR	Newly diagnosed diabetes	Known diabetes	*P* for difference
Oral antidiabetic drugs	—	—	—	59.9	
Antihypertensive drugs	49.3	47.5	44.7	62.0	<0.001
ACE inhibitors	13.8	14.0	17.8	16.7	0.29
Angiotensin II antagonists	13.6	10.5	11.2	22.1	<0.001
Calcium antagonists	21.9	21.6	20.1	34.1	<0.001
β-Blockers	26.1	23.9	28.1	37.0	<0.001
Diuretics	7.1	8.1	8.1	13.2	0.008
Lipid-lowering drugs	11.6	14.3	9.7	17.7	0.01
Antiplatelet drugs	20.7	20.6	18.8	24.3	0.33
Treatment of CAD (%)					
Coronary artery bypass graft	1.9	2.2	1.6	3.6	0.25
Percutaneous coronary intervention	43.6	52.2	62.8	58.2	<0.001

Data are mean (SE) or percentage, except that duration of CAD is shown as median (lower–upper quartiles); all continuous variables are adjusted for age and sex, except for age (adjusted for sex only).

normoglycemia. Chinese CAD patients with IGR were also associated with an increased risk of CVD mortality.

The current study found that the prevalence of diabetes and IGR in Chinese CAD patients was 45.4 and 23.3%. Our result was the same as the Euro Heart Survey and the China Heart Survey, which showed that almost half of CAD patients had diabetes and ~25% of CAD patients had IGR (3,4).

Only a few studies have assessed the association between hyperglycemia (including known and newly diagnosed diabetes, as well as IGR and IFG) and death risk among CAD patients. The current study indicated that known diabetes, newly diagnosed diabetes, and prediabetes (IGR or IFG) were independent risk factors of mortality among CAD patients. Several previous

Table 2—HRs for all-cause and cardiovascular mortality according to glucose states among CAD patients

Based on FPG and OGTT*	No. of participants	No. of deaths	Person-years	HR (95% CI) Model 1†	Model 2‡	Model 3§
All-cause mortality						
Normoglycemia	537	23	1,672	1	1	1
IGR	402	27	1,244	1.60 (0.92–2.79)	1.47 (0.84–2.57)	1.58 (0.90–2.77)
Newly diagnosed diabetes	366	37	1,055	2.68 (1.59–4.51)	2.52 (1.49–4.28)	2.41 (1.42–4.11)
Known diabetes	421	42	1,291	2.21 (1.33–3.67)	2.11 (1.26–3.52)	2.29 (1.36–3.84)
P value for trend				0.001	0.003	0.004
Cardiovascular mortality						
Normoglycemia	537	17	1,672	1	1	1
IGR	402	24	1,244	1.92 (1.03–3.57)	1.73 (0.92–3.23)	1.89 (1.01–3.54)
Newly diagnosed diabetes	366	31	1,055	3.02 (1.67–5.45)	2.85 (1.57–5.19)	2.74 (1.50–5.01)
Known diabetes	421	37	1,291	2.63 (1.48–4.68)	2.48 (1.39–4.42)	2.73 (1.52–4.91)
P value for trend				0.002	0.003	0.003
Based on FPG only						
All-cause mortality						
Normoglycemia	713	33	2,259	1	1	1
IFG	343	29	1,029	1.88 (1.14–3.11)	1.72 (1.04–2.84)	1.80 (1.09–2.98)
Newly diagnosed diabetes	249	25	683	2.47 (1.47–4.17)	2.35 (1.39–3.98)	2.15 (1.26–3.66)
Known diabetes	421	42	1,291	2.03 (1.29–3.20)	1.96 (1.24–3.11)	2.09 (1.31–3.33)
P value for trend				0.002	0.006	0.007
Cardiovascular mortality						
Normoglycemia	713	25	2,259	1	1	1
IFG	343	25	1,029	2.14 (1.23–3.72)	1.90 (1.09–3.33)	1.99 (1.14–3.49)
Newly diagnosed diabetes	249	22	683	2.85 (1.61–5.07)	2.70 (1.52–4.82)	2.48 (1.38–4.48)
Known diabetes	421	37	1,291	2.36 (1.42–3.93)	2.25 (1.35–3.76)	2.42 (1.44–4.06)
P value for trend				0.001	0.003	0.004

*All patients were measured for FPG (n = 1,726) and some patients conducted OGTT (n = 643). †Model 1 was adjusted for age and sex. ‡Model 2 was adjusted for model 1 covariates plus education, marriage, leisure-time physical activity, smoking, and alcohol drinking. §Model 3 was adjusted for model 2 covariates plus type, severity, duration, and treatment of CAD, history of heart failure, BMI, SBP, total cholesterol, HDL cholesterol, eGFR, and use of antihypertensive, cholesterol-lowering, and antiplatelet drugs.

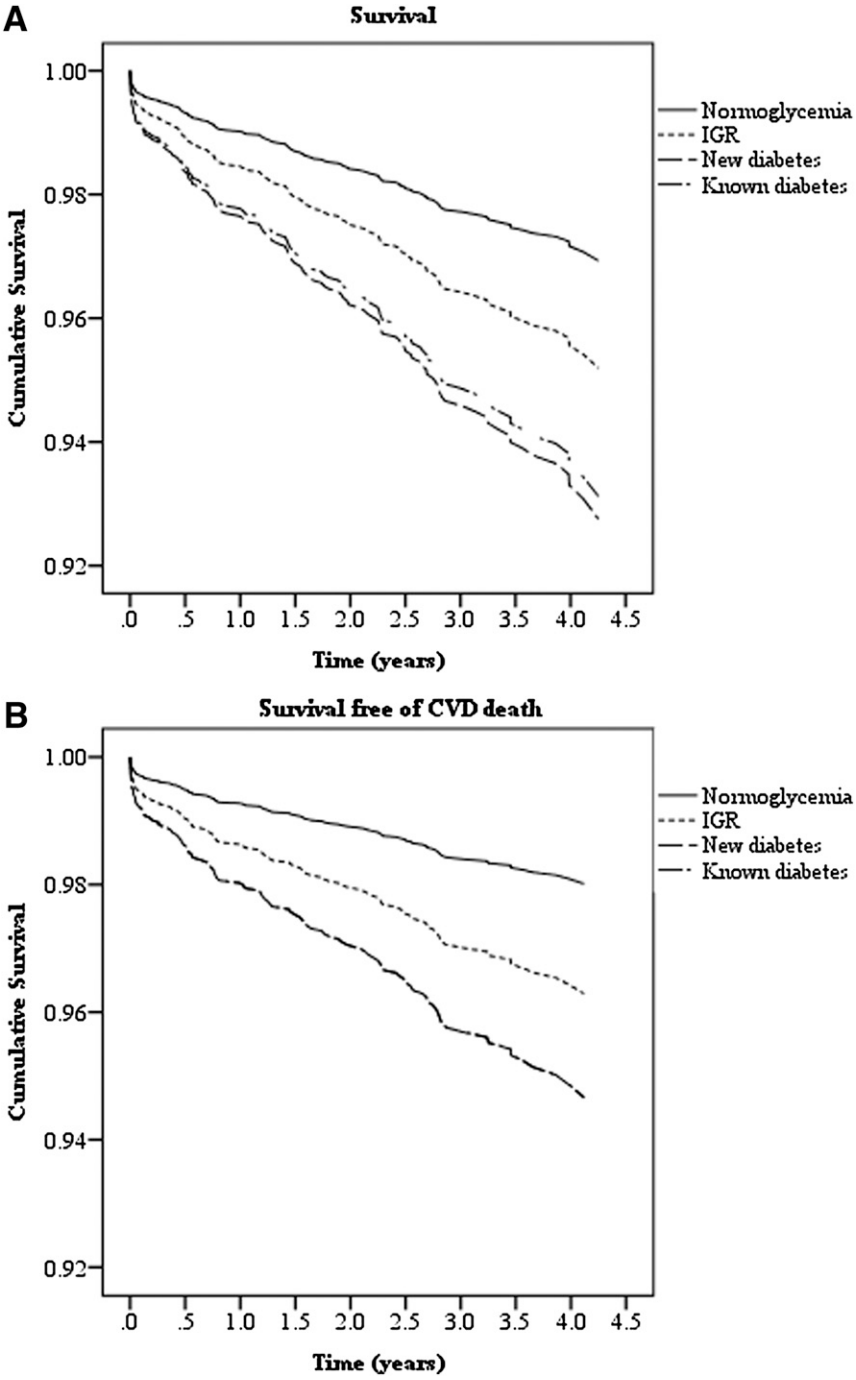

Figure 1—Multivariate-adjusted cumulative survival curves of all-cause (*A*) and CVD (*B*) mortality associated with both fasting and 2-h glucose states. Adjusted for age; sex; education; marriage; leisure-time physical activity; smoking; alcohol drinking; type, severity, duration, and treatment of CAD; history of heart failure; BMI; SBP; total cholesterol; HDL cholesterol; eGFR; and use of antihypertensive, cholesterol-lowering, and antiplatelet drugs. The line of newly diagnosed diabetes overlapped with the line of known diabetes in *B*.

studies have confirmed that known diabetes is associated with a high risk of adverse outcome for CAD patients (8,26). However, regarding newly diagnosed diabetes and IGR, previous findings were inconsistent. One Swedish study including 168 patients with acute myocardial infarction identified that abnormal glucose tolerance (combined newly diagnosed diabetes and IGT) was a prominent risk factor of further cardiovascular events (14). But with a small sample size (168 patients), this study did not analyze the newly diagnosed diabetes and IGT separately with further cardiovascular risk. In agreement with our results, two early American studies reported that among CAD patients, both IFG (FPG 6.1–6.9 mmol/L) and diabetes were associated with an increased risk of mortality compared with normoglycemia (27,28). In contrast with our study, they did not have OGTT measurements, so they could not further evaluate the risk of IGT and IGR. Although we used new ADA standards (FPG 5.6–6.9 mmol/L) to define IFG, this threshold still can predict an increased risk of mortality. Displayed by spline plots, we found a J-shaped relationship between the baseline FPG and subsequent death of all-cause and CVD; the cut point of increase in the risk was apparent for glucose level, which was below current diabetic threshold, even the IFG threshold. This finding was consistent with the previous Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe (DECODE) study. In their meta-analysis, there was a J-shaped relation between FPG and all-cause, CVD, and non-CVD mortality among European general populations. And the thresholds of increase of risk were 5.3 mmol/L for all-cause mortality and 5.4 mmol/L for CVD mortality (12). Thus, our study confirmed the prognostic significance of the current ADA recommendation for the lower IFG threshold in Chinese patients with CAD. The Euro Heart Survey found that only CAD patients with both known and newly diagnosed diabetes, but not with IGR, were at high risk of mortality during the 1-year follow-up period (13). Besides the different ethnicities, there were some other differences in the methods between our study and the Euro Heart Survey, which may result in this contrary conclusion. The Euro Heart Survey only focused on 1-year outcome, which may not be long enough to observe the difference in prognosis of the IGR group. Second, the Euro Heart Survey did not report the separate analysis on the classification of patients based on OGTT or FPG only due to small sample size. But they did

Table 3—HRs for all-cause and cardiovascular mortality according to CAD patients with both fasting and 2-h glucose *

	No. of participants	No. of deaths	Person-years	HRs (95% CIs) Model 1†	Model 2‡	Model 3§
All-cause mortality						
Normoglycemia	122	2	412	1	1	1
IGR	209	8	702	2.34 (0.50–11.0)	2.19 (0.46–10.4)	2.29 (0.48–10.9)
Newly diagnosed diabetes	366	37	1,055	6.55 (1.58–27.2)	6.11 (1.46–25.6)	5.59 (1.33–23.5)
Known diabetes	421	42	1,291	5.35 (1.29–22.1)	5.11 (1.23–21.2)	5.12 (1.23–21.3)
P value for trend				0.006	0.008	0.019
Cardiovascular mortality						
Normoglycemia	122	2	412	1	1	1
IGR	209	8	702	2.33 (0.49–11.0)	2.12 (0.45–10.0)	2.31 (0.48–11.0)
Newly diagnosed diabetes	366	31	1,055	5.42 (1.30–22.7)	4.96 (1.18–20.9)	4.57 (1.08–19.4)
Known diabetes	421	37	1,291	4.68 (1.12–19.4)	4.34 (1.04–18.1)	4.49 (1.07–18.8)
P value for trend				0.029	0.036	0.072
All-cause mortality						
Normoglycemia	122	2	412	1	1	1
Isolated IFG	37	3	121	6.48 (1.08–38.8)	5.83 (0.96–35.3)	5.81 (0.94–35.9)
Impaired glucose tolerance	172	5	581	1.69 (0.33–8.71)	1.59 (0.31–8.27)	1.69 (0.32–8.81)
Newly diagnosed diabetes	366	37	1,055	6.54 (1.57–27.2)	6.10 (1.46–25.5)	5.62 (1.33–23.6)
Known diabetes	421	42	1,291	5.34 (1.29–22.1)	5.11 (1.23–21.2)	5.13 (1.23–21.4)
P value for trend				0.008	0.011	0.024
Cardiovascular mortality						
Normoglycemia	122	2	412	1	1	1
Isolated IFG	37	3	121	6.47 (1.08–38.8)	5.41 (0.89–32.8)	5.48 (0.88–33.9)
Impaired glucose tolerance	172	5	581	1.68 (0.33–8.67)	1.55 (0.30–8.05)	1.73 (0.33–9.02)
Newly diagnosed diabetes	366	31	1,055	5.41 (1.29–22.6)	4.95 (1.17–20.8)	4.59 (1.08–19.5)
Known diabetes	421	37	1,291	4.66 (1.12–19.4)	4.34 (1.04–18.1)	4.51 (1.07–18.9)
P value for trend				0.029	0.040	0.077

*All patients were measured for both FPG and OGTT (n = 1,118). †Model 1 was adjusted for age and sex. ‡Model 2 was adjusted for model 1 covariates plus education, marriage, leisure-time physical activity, smoking, and alcohol drinking. §Model 3 was adjusted for model 2 covariates plus type, severity, duration, and treatment of CAD; history of heart failure; BMI; SBP; total cholesterol; HDL cholesterol; eGFR; and use of antihypertensive, cholesterol-lowering, and antiplatelet drugs.

observe a higher prevalence of mortality in IFG and IGT patients, although the differences remained insignificant.

The current study also showed that in comparison with known diabetic CAD patients, the risk of death from all causes and CVD was a little higher in newly diagnosed diabetic patients. This might be because not all the newly diagnosed patients were patients with new onset of diabetes. Some of them had diabetes for a period of time but were undiagnosed, which was proven by the Chinese high undiagnosed rate of diabetes (2). Lack of monitoring and control of glucose might partly explain the higher risk of mortality compared with known diabetic patients, 69% of whom took antidiabetic drugs at baseline in our cohort. Moreover, our patients with newly diagnosed diabetes had more severe CAD and shared more harmful lifestyles. The rates of smoking and alcohol drinking were higher and the physical activity time was less in patients with newly diagnosed diabetes.

Since IGR, IFG, and newly diagnosed diabetes have been confirmed as independent risk factors of death in our study and several others, we need to pay attention to CAD patients with hyperglycemia, especially those with prediabetes and newly diagnosed diabetes. IFG and IGT have been proven as high risk factors of developing diabetes, and they are considered as intermediate stages in any form of the diabetes process (29,30). In addition, subjects with IFG and IGT are also related to many traditional CVD risk factors, such as obesity, dyslipidemia, and hypertension. Recent studies have shown that the onset of diabetes can be prevented or delayed in subjects with prediabetes through lifestyle intervention and treatment with oral hypoglycemic agents, and lifestyle intervention is more effective than drugs (29–31). Therefore, it is important to develop a screening strategy for glucose that is both practical and predictive for individuals who will benefit from early diagnosis and prevention of glucose abnormality. Our finding also raises the question of whether directed glucose-lowering intervention might further improve clinical outcomes in CAD patients with hyperglycemia.

Several possible mechanisms may explain our results. Hyperglycemia itself may have direct cardiotoxicity that leads to worse prognosis in CAD patients. The effects include inducing electrophysiological alterations and fatal arrhythmias; reducing ischemic preconditioning, resulting in worse myocardial performance; increasing thrombophilia; intensifying inflammatory immune reactions; and worsening endothelial function (32). All these processes are related to bad

cardiac function and contribute to adverse outcomes.

There are some limitations in the present study. First, our subjects were enrolled from hospitals, which may bring about selection bias. In general, inpatients are considered as having a more severe disease status than nonhospitalized patients. However, we included both acute CAD patients and those with stable manifestation, and some of them were electively admitted patients with mild status. Thus, we can reduce the bias. Second, only some of the study samples conducted OGTTs due to the clinical practice rituals and patient will. To evaluate the impact of this shortcoming, we performed separate subgroup analyses in 1,118 CAD patients with both FPG and 2-h glucose measurements compared with 1,724 CAD patients of all our study samples with full FPG measurements and some 2-h glucose measurements. In general, the significant associations of known and newly diagnosed diabetes with all-cause and CVD mortality were not influenced substantially. But the HRs of IFG and IGT patients were statistically insignificant, which may be due to missing OGTTs of the high-risk patients. Third, we cannot completely exclude the effects of residual confounding resulting from measurement error in the assessment of confounding factors or some unmeasured factors.

In conclusion, our study confirms that IFG, newly diagnosed diabetes, and known diabetes are all associated with increased risks of all-cause and CVD mortality among CAD patients, and patients with IGR had significantly higher risk for CVD mortality and marginally greater risk for all-cause mortality.

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