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Prediabetes and long-term outcomes in patients with three-vessel coronary artery disease: A large single-center cohort study

Deshan Yuan, Ce Zhang, Sida Jia, Lin Jiang, Lianjun Xu, Yin Zhang, Jingjing Xu, Bo Xu, Rutai Hui, Runlin Gao, Zhan Gao, Lei Song, Jinqing Yuan*

National Center for Cardiovascular Diseases, Fu Wai Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Beijing, China

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***Correspondence**
Jinqing Yuan
Tel.: +86-108-8832-2451
Fax: +86-10-6833-3879
E-mail address:
dr_jinqingyuan@sina.com

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ABSTRACT

Aims/Introduction: Whether detection of prediabetes by routinely testing hemoglobin A_{1c} and fasting plasma glucose in three-vessel disease patients could identify individuals at high risk of future cardiovascular disease events remains unclear. This study evaluated the relationship between different glycemic status and clinical outcomes in this specific population.

Materials and Methods: This study included 8,891 Chinese patients with three-vessel disease. Patients were categorized according to their glycemic status (normoglycemia [NG], n = 3,195; prediabetes, n = 1,978; diabetes mellitus, n = 3,718).

Results: The median follow-up time was 7.5 years, during which 1,354 deaths and 2,340 major adverse cardiac and cerebrovascular events occurred. Compared with the NG group, patients in the prediabetes and diabetes mellitus groups had more comorbidities. After adjusting for confounders, the diabetes mellitus group had a higher risk of all-cause death (hazard ratio [HR] 1.36, 95% confidence interval [CI] 1.20–1.53; $P < 0.001$), cardiac death (HR 1.35, 95% CI 1.14–1.61; $P = 0.001$) and major adverse cardiac and cerebrovascular events (HR 1.22, 95% CI 1.11–1.34; $P < 0.001$) compared with the NG group, whereas the prediabetes and NG groups had no significant difference. The diabetes mellitus group also had a higher risk of stroke compared with the NG group (HR 1.22, 95% CI 1.02–1.46; $P = 0.031$).

Conclusions: In the context of three-vessel disease, prediabetes patients have comparable long-term outcomes in terms of major adverse cardiac and cerebrovascular events, cardiac death and all-cause death to those with NG. Routine screening of glycemic metabolism based on hemoglobin A_{1c} and fasting plasma glucose might be valuable to identify individuals with diabetes mellitus who are at high risk of future cardiovascular disease events and individuals with prediabetes who are at high risk of progressing to diabetes mellitus.

INTRODUCTION

Coronary artery disease (CAD) is the major cause of cardiovascular death worldwide[1]. Regarded as a severe type of CAD, three-vessel disease (3VD) presents in nearly 30% of CAD patients[2,3], which is also a significant risk factor for worse outcomes[4]. Diabetes mellitus is a proven primary and secondary risk factor for CAD[5,6]. Substantial evidence shows that even abnormal glycemic levels below the diagnostic criteria for diabetes are also involved in the development of CAD[7–9]. Prediabetes represents an intermediate status in the progression from normoglycemia (NG) to diabetes[10]. Although diabetes has been intensively studied in the context of multivessel diseases[11–13], whether prediabetes could affect outcomes of patients with 3VD remains unclear. According to the latest guidelines[14,15], prediabetes can be detected by measuring fasting plasma glucose (FPG) and hemoglobin A_{1c} (HbA_{1c}), an established surrogate indicator of glycemia during the previous 2–3 months. Although the oral glucose tolerance test (OGTT) is a well-

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known method to evaluate glycemic metabolism, its application is rather inconvenient in routine clinical practice, and shows poor repeatability and compliance. Instead, the combined determination of HbA_{1c} and FPG is simpler and more reproducible, and confers favorable advantages of screening both for the diagnosis of diabetes and prediabetes, with superior performance of diagnostic sensitivity and specificity[16,17]. Taken together, this study aimed to evaluate the potential relationship between prediabetes assessed by FPG and HbA_{1c} and long-term clinical outcomes in 3VD patients based on a real-world, prospective observational cohort of Chinese patients.

METHODS

Study population

The present study was carried out based on a prospective observational cohort of 8,943 Chinese 3VD patients. 3VD was defined as three main coronary arteries, including the right coronary artery, left circumflex artery and left anterior descending artery, all having stenosis of >50% confirmed by coronary angiography. The consecutive enrollment of patients was completed at Fu Wai Hospital, Beijing, China, from 2004 to 2011. Patients received either revascularization or medical treatment alone according to contemporary practice guidelines, judgments from a team of clinical cardiologists and their own preference[18,19]. The follow up and collection of baseline and procedural data for all participants were completed by independent clinical research coordinators. The study was approved by the ethics committee of Fu Wai Hospital, and followed the principles of the Declaration of Helsinki. All participants gave written informed consent.

Glycemic categories were based on the latest guideline recommendations[15]. Diabetes was defined as newly diagnosed diabetes (FPG ≥7.0 mmol/L or HbA_{1c} ≥6.5%) or known diabetes. Prediabetes was defined by FPG 5.6–6.9 mmol/L or HbA_{1c} levels ranging from 5.7 to 6.4%. NG was defined by HbA_{1c} levels <5.7% and FPG <5.6 mmol/L.

Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg for three or more consecutive times, and/or current use of antihypertensive medication. Fasting total cholesterol ≥5.2 mmol/L, low-density lipoprotein cholesterol ≥3.4mmol/L, triglyceride ≥1.7 mmol/L, high-density lipoprotein cholesterol <1.0 mmol/L and/or chronic use of lipid-lowering drugs were considered criteria for hyperlipidemia. Chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for >3 months using the Chronic Kidney Disease Epidemiology Collaboration equation[20].

Blood samples of all participants were collected from the antecubital vein after a 12-h fast. HbA_{1c} was measured using the G8 HbA_{1c} standard analysis model.

Outcomes

Survival data were collected through a phone call, outpatient visit or follow-up letter. A group of clinical doctors checked and verified all events independently and carefully. The primary end-point was all-cause death. Secondary end-points included cardiac death and major adverse cardiac and cerebrovascular events (MACCE), which consisted of all-cause death, myocardial infarction (MI) and stroke. There is no international consensus on the definition of cardiac death, and previous studies have defined it as any death without a clear non-cardiac cause. We referred to this definition and considered all deaths were cardiac unless an unequivocal non-cardiac cause could be established.

Statistical analysis

Categorical variables were summarized as the frequency and percentage, and continuous variables were expressed as the mean ± standard deviation. Pearson's χ^2-test or Fisher's exact test were used to compare differences for categorical variables, and analysis of variance or the Kruskal–Wallis test followed by post-hoc tests (Bonferroni or Mann–Whitney *U*-test) were used to compare differences for continuous variables. The Kaplan–Meier method was used to construct survival curves, and the log–rank test was used to compare differences among groups. We exerted univariable and multivariable Cox proportional hazards regressions to evaluate the relationship between different glycemic status and long-term outcomes. The covariates adjusted in the multivariable analysis including: sex, history of smoking, previous stroke, hypertension, age, peripheral artery disease, hyperlipidemia, left main disease, chronic kidney disease, body mass index, treatment strategy, left ventricular ejection fraction (LVEF), clinical presentation and SYNTAX score (≤22, 23–32 or ≥33). Exploratory subgroup analysis was carried out to assess the effect of glycemic status (NG and Prediabetes) on MACCE and all-cause death in specific patient subsets using aforementioned the multivariable model. Potential subgroup difference was interpreted by testing interactions between glycemic status and these covariates. A two-tailed *P*-value of <0.05 was considered to be statistically significant. All of the analyses were carried out with IBM® SPSS® statistics version 25.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline patient characteristics

The present study included 8,891 Chinese patients with 3VD, the FPG and HbA_{1c} data of which were available (Figure 1). Table 1 shows the baseline characteristics of the patients. Compared with the NG group, patients in the prediabetes and diabetes group tended to be older, women, and have higher levels of triglyceride and body mass index. Diabetes and prediabetes patients presented a higher incidence of comorbidities (i.e., hyperlipidemia, peripheral artery disease and previous stroke), but they were less likely to undergo percutaneous coronary intervention. In addition, patients with diabetes and prediabetes were more prone to acute coronary syndrome (ACS). Patients in the prediabetes group had higher low-density lipoprotein cholesterol and total cholesterol levels, as compared with those

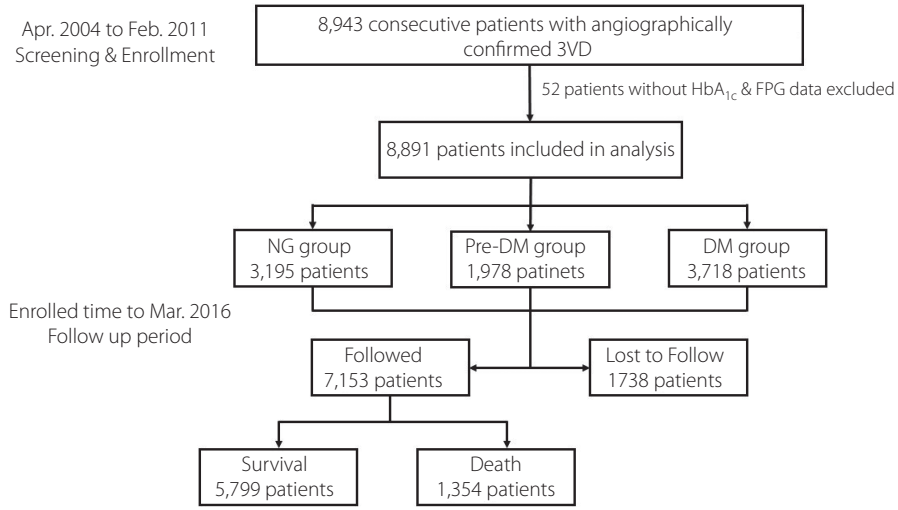

Figure 1 | A flow chart for participant selection. 3VD, three-vessel disease; DM, diabetes mellitus; FPG, fasting plasma glucose; HbA_{1c}, hemoglobin A1c; NG, normoglycemia; Pre-DM, prediabetes.

in the NG group. Patients in the diabetes group had a lower rate of smoking, lower LVEF and high-density lipoprotein cholesterol levels, and higher SYNTAX scores than both the NG and prediabetes group.

Clinical outcomes

The follow-up rate was 80.5% during a median follow-up time of 7.5 years (interquartile range 5.9–9.1 years; Tables S1,S2). Those lost to follow up were older with a higher prevalence of previous stroke, previous MI, worse creatinine clearance and more left main coronary artery disease. During the follow-up period, there were 1,354 deaths, of which 688 (50.8%) were cardiac, and 2,340 MACCEs occurred. The incidence of cardiac death, MACCE and all-cause death was lower in the prediabetes group than the diabetes group. Compared with the NG group, the prediabetes group had a lower incidence of MACCE and MI, whereas the diabetes group had a higher incidence of cardiac death, MACCE and all-cause death, and lower incidence of MI (all $P < 0.05$; Table 1). The primary and secondary end-points estimated by Kaplan–Meier analysis are shown in Figure 2 (log–rank $P < 0.001$ for MACCE, cardiac death and all-cause death).

The results of univariable and multivariable analyses showed that the risk for MI, stroke, MACCE, cardiac death and all-cause death did not differ between the prediabetes and NG group (Table 2). The diabetes group had a higher risk of cardiac death (adjusted hazard ratio [HR] 1.35, 95% confidence interval [CI] 1.14–1.61; $P = 0.001$), MACCE (adjusted HR 1.22, 95% CI 1.11–1.34; $P < 0.001$) stroke (adjusted HR 1.22, 95% CI 1.02–1.46; $P = 0.031$) and all-cause death (adjusted HR 1.36, 95% CI 1.20–1.53; $P < 0.001$) than patients with NG, as well as a higher risk of MACCE (adjusted HR 1.24, 95% CI 1.11–1.38; $P < 0.001$), cardiac death (adjusted HR 1.28, 95% CI 1.04–1.56; $P = 0.019$) and all-cause death (adjusted HR 1.39, 95% CI 1.20–1.61; $P < 0.001$) than patients with prediabetes.

Subgroup analysis showed no significant interactions regarding all-cause death and MACCE between glycemic status and those covariates (treatment strategy, SYNTAX score, sex, age, left main disease, LVEF and clinical presentation, all P for interaction >0.05; Figure 3).

DISCUSSION

The present large single-center observational study is the first investigation of the association of prediabetes and long-term clinical outcomes of 3VD patients. The major findings are summarized as follows: (i) no significant difference was observed for the risk of MACCE, cardiac death and all-cause death between the prediabetes and NG group; and (ii) the diabetes group had a higher risk of MACCE, cardiac death and all-cause death compared with patients in NG and prediabetes group.

The risk of death conferred by 3VD is nearly twice than that of single-vessel CAD[4]. It is still essential to investigate potential risk factors affecting the clinical outcomes of 3VD patients, and further develop early appropriate intervention strategies to achieve better clinical outcomes. Impaired glycemic metabolism, including diabetes and prediabetes, is common among patients with 3VD. Similar to diabetes, prediabetes is also associated with the development of CAD[8,9]. The exact pathophysiological mechanisms underlying this association might include atherosclerosis, inflammation, insulin resistance, endothelial dysfunction and abnormal activation of platelets[21–23]. However, limited studies have specifically investigated the predictive value of prediabetes in the clinical outcomes of CAD population, especially in the context of 3VD.

Because of the complexity of applying OGTT in routine clinical practice, we combined FPG and HbA_{1c} together to detect

Table 1 | Baseline characteristics of the study population

	NG (n = 3,195)	Pre-DM (n = 1,978)	DM (n = 3,718)
Age (years)	60.4 ± 10.3	61.4 ± 10.0*	61.5 ± 9.7*
Male	2,700 (84.5)	1,596 (80.7)*	2,786 (74.9)*†
BMI (kg/m^2)	25.6 ± 3.0	26.0 ± 3.2*	26.0 ± 3.0*
Previous MI	1,139 (35.6)	694 (35.1)	1,330 (35.8)
Previous revascularization	704 (22.0)	418 (21.1)	809 (21.8)
Previous stroke	257 (8.0)	199 (10.1)*	427 (11.5)*
Hypertension	2,078 (65.0)	1,330 (67.2)	2,606 (70.1)*
Hyperlipidemia	1,576 (49.3)	1,226 (62.0)*	2,173 (58.4)*†
COPD	32 (1.0)	18 (0.9)	50 (1.3)
PAD	168 (5.3)	180 (9.1)*	341 (9.2)*
CKD	19 (0.6)	10 (0.5)	44 (1.2)*†
Current/former smoker	1,901 (59.5)	1,128 (57.0)	1,923 (51.7)*†
Clinical presentation			
SAP	1,208 (37.8)	671 (33.9)*	1,287 (34.6)*
ACS	1,987 (62.2)	1,307 (66.1)*	2,431 (65.4)*
LVEF (%)	59.1 ± 8.8	58.9 ± 9.4	57.6 ± 9.6*†
Laboratory analyses			
HbA_{1c} (%)	5.2 ± 0.4	5.9 ± 0.4*	7.3 ± 1.5*†
Number with HbA_{1c}	789 (24.7)	1,261 (63.8)	2,427 (65.3)
Fasting glucose (mmol/L)	5.0 ± 0.5	5.6 ± 0.7*	7.5 ± 2.7*†
Number with fasting glucose	3,195 (100%)	1,978 (100%)	3,718 (100%)
Total cholesterol (mmol/L)	4.56 ± 1.01	4.66 ± 1.10*	4.58 ± 1.09
HDL-C (mmol/L)	1.06 ± 0.25	1.05 ± 0.29	1.02 ± 0.25*†
LDL-C (mmol/L)	2.54 ± 0.78	2.62 ± 0.88*	2.53 ± 1.01†
Triglycerides (mmol/L)	1.61 ± 0.84	1.78 ± 0.88*	1.90 ± 1.26*
CCr (mL/min)*,‡	85.0 ± 26.1	85.5 ± 26.1	85.8 ± 27.8
Left main involvement	724 (22.7)	443 (22.4)	896 (24.1)
SYNTAX score†,§			
≤22	1,355 (42.6)	798 (40.5)	1,380 (37.3)*†
23–32	1,091 (34.3)	719 (36.5)	1,354 (36.6)
≥33	734 (23.1)	453 (23.0)	970 (26.2)*†
Treatment strategy			
PCI	1,454 (45.5)	815 (41.2)*	1,532 (41.2)*
CABG	933 (29.2)	630 (31.9)	1,119 (30.1)
MT	808 (25.3)	533 (26.9)	1,067 (28.7)*
Medication at discharge			
Aspirin	3,063 (95.9)	1,885 (95.3)	3,551 (95.5)
Clopidogrel	1,651 (51.7)	1,067 (53.9)	1,926 (51.8)
ACEI	1,191 (37.3)	689 (34.8)	1,406 (37.8)
ARB	381 (11.9)	285 (14.4)*	689 (18.5)*†
β-Blocker	2,777 (86.9)	1,735 (87.7)	3,301 (88.8)
CCB	1,178 (36.9)	658 (33.3)*	1,376 (37.0)†
Statin	2,126 (66.5)	1,317 (66.6)	2,500 (67.2)
End-points			
All-cause death	448 (14.0)	240 (12.1)	666 (17.9)*†
Cardiac death	221 (6.9)	129 (6.5)	338 (9.1)*†
MACCE	827 (25.9)	437 (22.1)*	1,076 (28.9)*†
MI	219 (6.9)	91 (4.6)*	203 (5.5)*
Stroke	220 (6.9)	137 (6.9)	283 (7.6)

ACEI, angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin II receptor blockers; BMI, body mass index; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CCr, creatinine clearance; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; MT, medical therapy; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SAP, stable angina pectoris. *Values are presented as the mean ± standard deviation or number (%). $P < 0.05$ versus normoglycemia (NG). †$P < 0.05$ versus prediabetes (Pre-DM). Hypertension was defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg for three or more consecutive times, and/or current use of antihypertensive medication. Fasting total cholesterol ≥5.2 mmol/L, low-density lipoprotein cholesterol (LDL-C) ≥3.4 mmol/L, triglyceride ≥1.7 mmol/L, high-density lipoprotein cholesterol (HDL-C) <1.0 mmol/L and/or chronic use of lipid-lowering drugs were considered criteria for hyperlipidemia. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for >3 months using the Chronic Kidney Disease Epidemiology Collaboration equation. ‡Calculated using the Cockcroft and Gault formula. §Calculated using an online calculator (http://www.syntaxscore.com) by a dedicated research group blinded to the clinical data.

diabetes and prediabetes, both of which are recommended by the latest guidelines[14,15]. During >7 years of follow up, we found no significant difference between the NG and prediabetes group in terms of MACCE, cardiac death and all-cause death, although the prediabetes group seemed to have worse baseline characteristics. Specifically, prediabetes patients were older, and more likely to have hyperlipidemia, peripheral artery disease and prior stroke, with a higher proportion of ACS. They also had higher level of body mass index, total cholesterol, low-density lipoprotein cholesterol and triglyceride compared with the NG population. The results previously documented in the literature are conflicting regarding the relationship between prediabetes and prognosis in non-diabetic CAD patients. In a prespecified analysis based on the Comparison of BIOdegradable Polymer and DuRablE Polymer Drug-eluting Stents in an All COmeRs PopulaTion (BIO-RESORT) trial[24], prediabetes was associated with an increased risk of cardiovascular events with 1-year follow up than NG in patients undergoing percutaneous coronary intervention. Another retrospective cohort study reported that during 2.8 years of follow up, prediabetes increased major adverse cardiac events risk in non-diabetic patients with MI[25]. Giraldez *et al.*[26] found prediabetes patients had similar outcomes of 30-day death and MI to those with normoglycemia in the ACS population. The Providing Regional

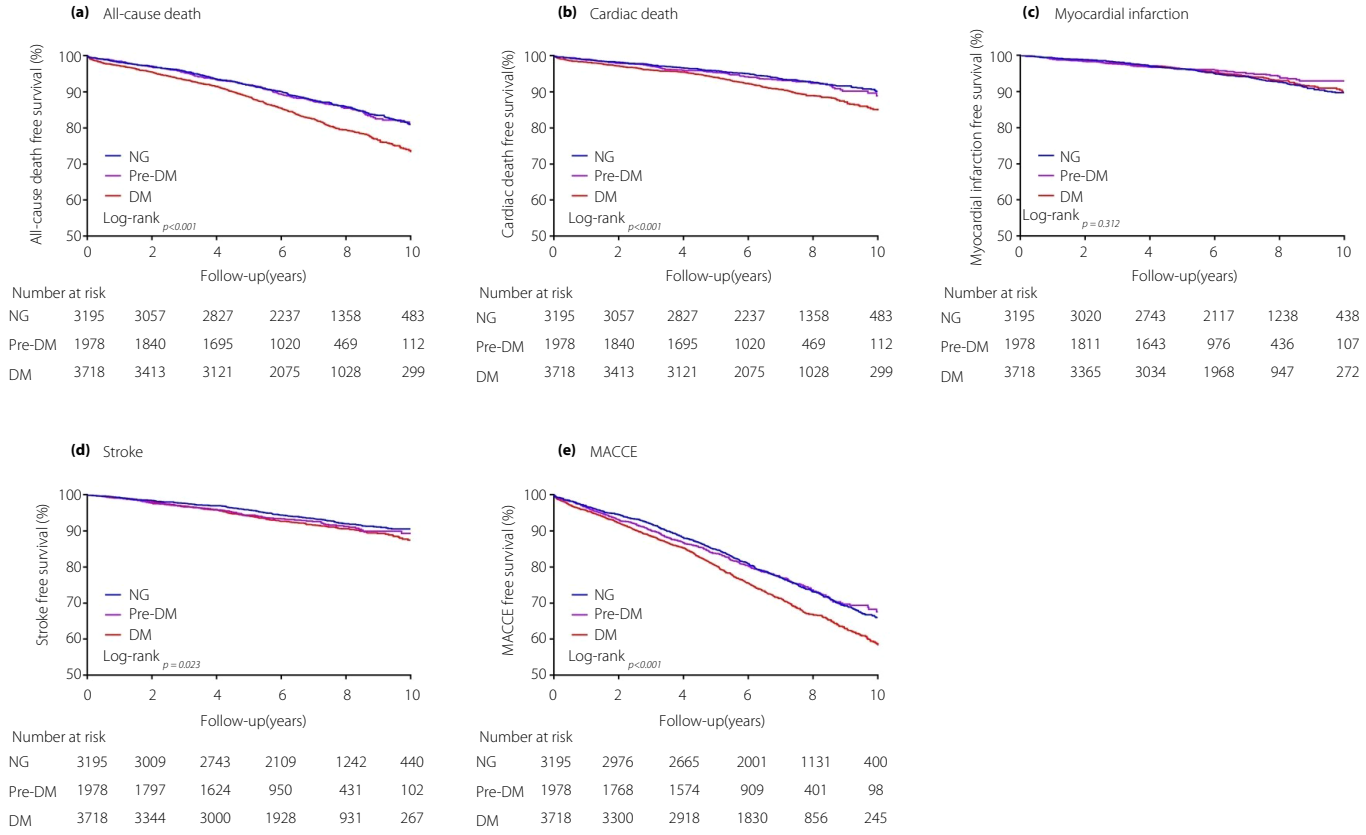

Figure 2 | Cumulative survival curves for the primary and secondary end-points in the three groups. Cumulative incidence curves for (a) all-cause death, (b) cardiac death, (c) myocardial infarction, (d) stroke and (e) major adverse cardiac and cerebrovascular events (MACCE). Blue represents normoglycemia (NG), purple represents prediabetes (Pre-DM) and red represents diabetes (DM).

Table 2 | Risk of primary and secondary outcomes

	All-cause death (n = 1,354)	Cardiac death (n = 688)	MACCE (n = 2,340)	MI (n = 513)	Stroke (n = 640)
Univariate analysis					
NG	1.00	1.00	1.00	1.00	1.00
Pre-DM	1.05 (0.90–1.23)	1.14 (0.92–1.42)	1.03 (0.91–1.15)	0.83 (0.65–1.06)	1.20 (0.97–1.48)
DM	1.50 (1.33–1.69)*†	1.54 (1.30–1.83)*†	1.31 (1.20–1.43)*†	0.95 (0.78–1.15)	1.29 (1.08–1.53)*
Multivariate analysis‡					
NG	1.00	1.00	1.00	1.00	1.00
Pre-DM	0.98 (0.83–1.45)	1.05 (0.84–1.31)	0.98 (0.88–1.11)	0.84 (0.66–1.08)	1.14 (0.92–1.42)
DM	1.36 (1.20–1.53)*†	1.35 (1.14–1.61)*†	1.22 (1.11–1.34)*†	0.96 (0.79–1.17)	1.22 (1.02–1.46)*

DM, diabetes mellitus; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction. *P < 0.05 versus normoglycemia (NG). †P < 0.05 versus prediabetes (Pre-DM). ‡Adjusted for age, sex, body mass index, previous stroke, hyperlipidemia, hypertension, peripheral artery disease, chronic kidney disease, smoke history, clinical presentation (stable angina pectoris or acute coronary syndrome), left main disease, left ventricular ejection fraction, SYNTAX score (≤22, 23–32 or ≥33) and treatment strategy (percutaneous coronary intervention, coronary artery bypass grafting or medical therapy).

Observations to Study Predictors of Events in Coronary Tree (PROSPECT) study also found prediabetes was not related to an increased risk of major adverse cardiac events in ACS patients[27]. However, the follow-up periods of the aforementioned studies were relatively short. The latest Prediction of Cardiovascular Events in Type 2 Diabetic Patients With Coronary Artery Disease- Application of Novel Risk Markers and Technology (ARTEMIS) study showed that prediabetes

had similar long-term cardiac mortality and major adverse cardiac events compared with NG in 1,948 CAD patients undergoing revascularization or optimal medical therapy with a follow-up period of >6 years[28]. The findings of the present study support and extend this result, and indicate that prediabetes screened based on HbA_{1c} and FPG might not worsen the long-term prognosis in 3VD patients. A possible hypothesis is that prediabetes represents the early stage of glycemic disturbance and has fewer end-organ effects than diabetes.

The present study also showed that the diabetes group was at a distinctly higher risk of long-term MACCE, cardiac death and all-cause death than both prediabetes and NG group, suggesting that particular attention should be paid to this high-risk population. 3VD patients should be carefully screened for undiagnosed diabetes, as diabetes patients have relatively more extensive CAD and worse outcomes as compared with those without diabetes. Prevention and long-term optimized management of diabetes is an important strategy to improve the prognosis of 3VD patients.

The prevalence of prediabetes is increasing worldwide. More than 470 million individuals were predicted to have from prediabetes in 2030[29]. In China, a national cross-sectional survey reported that the estimated prevalence of prediabetes was up to 35.7%[30]. Even worse, prediabetes patients are at higher risk of progressing to diabetes and metabolic disorders than individuals with normoglycemia[29], which will undoubtedly impose heavy health and economic burdens on the whole society. Given the remarkably high risk of MACCE, cardiac death and all-cause death in 3VD patients with diabetes, and high risk of prediabetes progression to diabetes, early identification and interventions of prediabetes patients are equally as important as those for diabetes patients in the 3VD population. Considering the limited use of OGTT for population screening in clinical practice, routine assessment of abnormal glycemic metabolism with testing of both HbA_{1c} and FPG where possible seems a simpler and more efficient measure[31,32]. Lifestyle and pharmacological interventions implemented early in the progression from prediabetes to diabetes might help delay or prevent the onset of diabetes, and further improve long-term clinical outcomes[33–36].

A series of subgroup analysis was carried out to further investigate whether prediabetes has an impact on some clinical

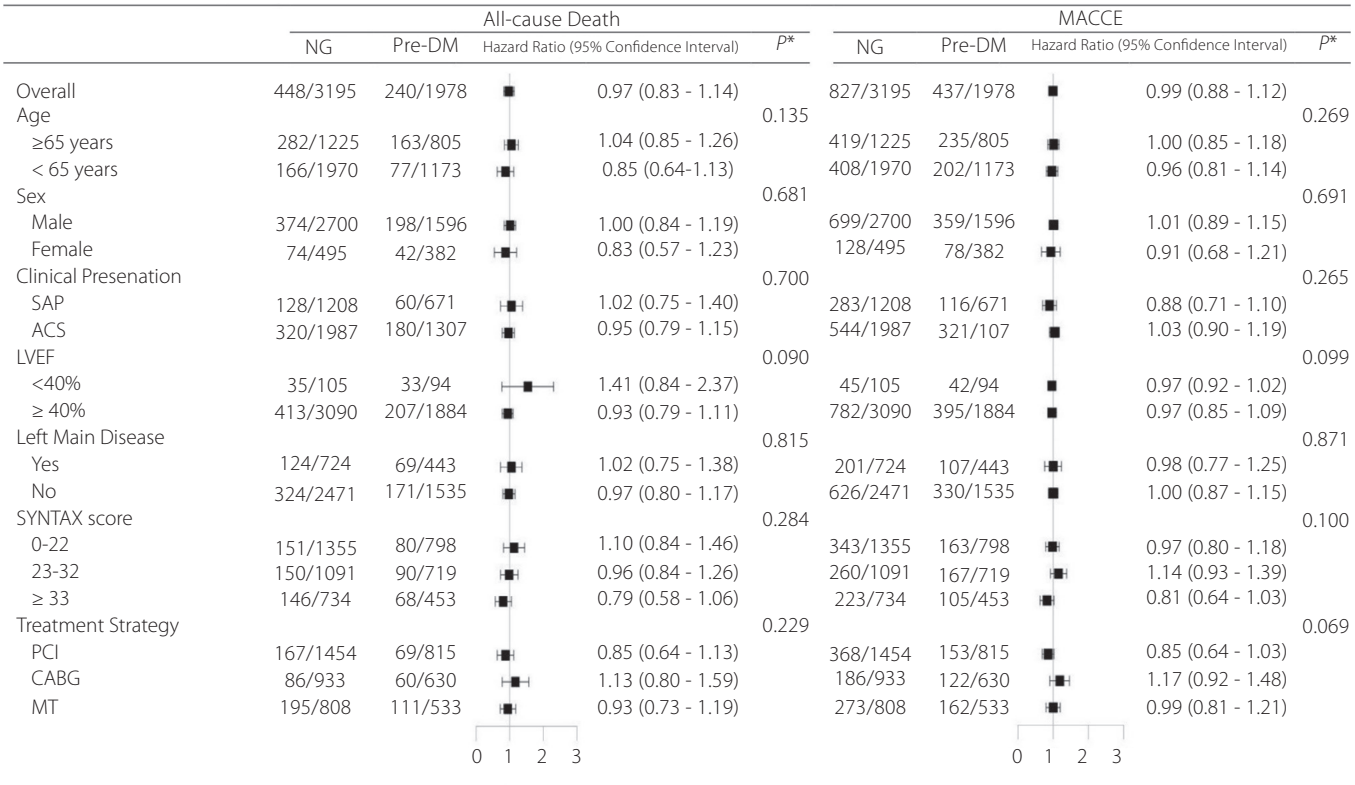

Figure 3 | Subgroup analysis of all-cause death and major adverse cardiac and cerebrovascular events (MACCE) between prediabetes (Pre-DM) and normoglycemia (NG). Hazard ratios and 95% confidence intervals were calculated by reference to the NG group. The interaction between different glycemic status (NG and Pre-DM) and each covariate was tested by a multivariable Cox proportional hazards regression model. ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; SAP, stable angina pectoris; LVEF, left ventricular ejection fraction; MT, medical therapy; PCI, percutaneous coronary intervention.

subgroups. The comparable results between the prediabetes and NG group in terms of MACCE and all-cause death were consistent across all subgroups including sex, age, LVEF, clinical presentation, left main disease, SYNTAX score and treatment strategy.

The present study had several shortcomings. First, this was a post-hoc analysis of a prospective Chinese cohort study where participants came from a single center and nearly 20% of them were lost to follow-up, and approximately half of the patients received a HbA_{1c} test, so the reliability and the generalization of the results might be limited. Therefore, more studies are warranted in the future to further confirm the present findings. Second, the OGTT was not routinely carried out at our center, so we combined HbA_{1c} and FPG together to detect diabetes and prediabetes in the analysis to ensure the results could be generalizable as much as possible to common clinical settings. Third, formal glycemic evaluation to identify new-onset diabetes and prediabetes was not available during the study period, which might slightly impair the strength of the present study. Fourth, antidiabetic agents could trigger cardiovascular events by means of hypoglycemia in patients with diabetes. However, we were unable to collect detailed data previously. Fifth, there might be some bias in the grouping of participants on the borderline of normal/prediabetes and prediabetes/diabetes, especially when using fasting plasma glucose. Sixth, assuming all deaths were cardiac unless an unequivocal non-cardiac cause was established might overestimate cardiac deaths.

In the context of 3VD, prediabetes patients have comparable long-term outcomes in terms of MACCE, cardiac death and all-cause death to those with NG. Routine screening of glycemic metabolism based on HbA_{1c} and FPG might be valuable to identify individuals with diabetes who are at high risk of future CVD events, and individuals with prediabetes who are at high risk of progressing to diabetes.

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DISCLOSURE

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Baseline characteristics of participants who were followed up.
Table S2 | Baseline characteristics of participants who were lost to follow up.