Impacts of Prediabetes Mellitus Alone or Plus Hypertension on the Coronary Severity and Cardiovascular Outcomes

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Abstract —Whether prediabetes mellitus (Pre-DM) alone or combined with hypertension is an independent risk factor for cardiovascular disease has not been fully clarified. This study aimed to further confirm whether the relation of Pre-DM to cardiovascular disease differs between individuals with or without hypertension. A total of 7121 consecutive patients with angina-like chest pain who received coronary angiography were evaluated and 4193 patients with angiography-proven stable, new-onset coronary artery disease were enrolled into the study. They were divided into 3 groups according to diabetes mellitus status and further stratified by hypertension. The severity of coronary artery disease was assessed by number of diseased vessels and Gensini score. All subjects were regularly followed up for the occurrence of the composite end points. Comparisons of coronary artery disease severity and outcomes were performed among these groups. During an average of 11 338 patient-years of follow-up, 434 (10.35%) cardiovascular events occurred. No significant difference was observed in coronary severity and composite end point events between Pre-DM and normal glucose regulation groups (both $P>0.05$). However, when hypertension was also incorporated as a stratifying factor, cardiovascular disease risk, assessed by coronary severity and clinical prognosis, was significantly elevated in Pre-DM plus hypertension and diabetes mellitus plus hypertension groups, compared with the reference group with normal glucose regulation and normal blood pressure (all $P<0.05$). The present study indicated that among patients with stable, new-onset coronary artery disease, the increased cardiovascular risk with Pre-DM is largely driven by the coexistence of hypertension rather than Pre-DM per se. **(*Hypertension*. 2018;71:1039-1046. DOI: 10.1161/HYPERTENSIONAHA.118.11063.)** ● **Online Data Supplement**

Key Words: coronary artery disease ■ diabetes mellitus ■ hypertension ■ prognosis ■ risk factors

Prediabetes mellitus (Pre-DM) refers to an intermediate metabolic state between normal glucose regulation (NGR) and diabetes mellitus (DM), including those with impaired glucose tolerance and impaired fasting glucose (IFG).[1] The growing obesity epidemic in the United States has been inescapably correlated with a surge in rates of pre-DM, and it has been called America's largest healthcare epidemic.[2] The prevalence of pre-DM in the American adults is steadily increasing, with an estimated rate reaching 36.2% in 2010.[3] Meanwhile, it was reported that ≈35.7% of the Chinese adult population had pre-DM and 10.9% had DM in a cross-sectional survey conducted in 2013 in mainland China.[4] The population with pre-DM is at a high risk of developing DM. Moreover, cardiovascular disease (CVD) is one of the most common chronic diseases worldwide with a high morbidity and mortality. The risk of CVD in patients with DM is 2 to 3 times higher than that of the NGR population.[5] The predisposition of pre-DM to DM makes it a potential risk factor for CVD as well. However, studies on the association between the stage of pre-DM and CVD risk were insufficient and failed to reach a general consensus.[5–10]

Noteworthily, few studies were found to combine pre-DM and hypertension together in the analysis for predicting CVD risk.[6,11] Moreover, to the best of our knowledge, there have been no studies to explore the impact of hypertension on the association between pre-DM and CVD risk, including coronary severity and clinical outcomes in patients with angiography-proven stable, new-onset coronary artery disease (CAD). Therefore, we conducted this prospective study in a large cohort of this population with 2 aims: (1) to explore the association between pre-DM and coronary severity and CVD outcomes and (2) to investigate whether pre-DM alone or coexistent with hypertension, defined according to the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7),[12] could significantly exacerbate CVD risk. Given the recent publication of 2017 American College of Cardiology/American Heart Association (ACC/AHA) guideline,[13] which

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redefines hypertension with a lower criterion, we also added this change to our study.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design and Population

This study complied with the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001, and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Each participant provided written, informed consent before enrollment.

From March 2011 to July 2016, 7164 consecutive Chinese patients, who received coronary angiography because of angina-like chest pain or positive treadmill exercise test or significant stenosis indicated by coronary computed tomography angiography, were considered for this analysis. On admission, 43 patients declined to participate. Next, based on elevated myocardial enzyme levels (cardiac troponin I [cTnI], creatine kinase [CK], and creatine kinase isoenzyme [CK-MB]), typical ECG changes, positive findings by coronary angiography, and medical history, 787 non-CAD patients and 1937 CAD patients who had acute coronary syndrome, previous myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting were excluded. Furthermore, 175 patients were rejected according to the exclusion criteria as follows: missing detailed laboratory data; uncontrolled decompensated heart failure; unstable hemodynamic status; thyroid dysfunction; infectious or systematic inflammatory disease; severe hepatic or renal insufficiency or malignant disease. During the study, 29 patients were lost to follow-up. Thus, the resulting population consisted of 4193 subjects with stable, new-onset CAD. According to their DM status, patients were classified into 3 groups: NGR (n=898), pre-DM (n=1805), and DM (n=1490; Figure 1), and then they were further stratified by the presence or absence of hypertension. The enrolled CAD patients were assigned to take optimal medical treatment or combined percutaneous coronary intervention/coronary artery bypass grafting and medical treatment. Details of the measurements and biochemical analysis and evaluation of CAD severity are contained in the online-only Data Supplement.

Definition of DM, Pre-DM, and Hypertension

Diagnosed DM was defined as a self-reported diagnosis that was determined previously by a specialist, or patients were being treated with hypoglycemic medications currently. Undiagnosed DM and pre-DM was defined according to the American Diabetes Association criteria.[1] Undiagnosed DM was confirmed by a fasting plasma glucose level ≥7.0 mmol/L (126 mg/dL), 2-hour glucose level ≥11.1 mmol/L (200 mg/dL), or hemoglobin A1c (HbA1c) level ≥6.5%.[1] Total DM was the sum of the number of patients with diagnosed DM and undiagnosed DM. Pre-DM was diagnosed as any participants who did not have DM but had a fasting plasma glucose ranges from 5.6 to <7.0 mmol/L (100–126 mg/dL), 2-hour glucose ranges from 7.8 to <11.1 mmol/L (140–200 mg/dL), or HbA1c level ranges from 5.7% to <6.5%.[1] NGR referred to the people who had neither pre-DM nor DM. Diagnosed hypertension was defined as a self-reported hypertension and currently taking antihypertensive drugs. Undiagnosed hypertension was defined according to the JNC-7 and 2017 ACC/AHA guidelines, respectively. Based on the JNC-7 criteria, patients with systolic blood pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg were diagnosed with hypertension.[12] According to the 2017 ACC/AHA guideline, patients with systolic BP ≥130 mm Hg or diastolic BP ≥80 mm Hg were defined as having hypertension.[13] Similarly, total hypertension was the sum of the number of patients with diagnosed hypertension and undiagnosed hypertension.

Follow-Up

After the initial appointment, all patients were actively followed-up at 6-month intervals thorough telephone communications and/or face-to-face interviews after hospital discharge by well-trained nurses or cardiologists who were blinded to the aim of this study. The follow-up time interval was counted from the enrollment till the last traceable hospital inpatient or outpatient record or telephone interview before August 2017. The primary end points were the all-cause death (death mainly caused by CVDs), nonfatal myocardial infarction, stroke, unplanned revascularization and hospitalized unstable angina. All available relevant data from any reported possible event were collected. Death of a participant was reported by relatives, the general practitioner, or the specialist who treated the participant. Three experienced cardiologists who were masked to any of the study data classified the events independently.

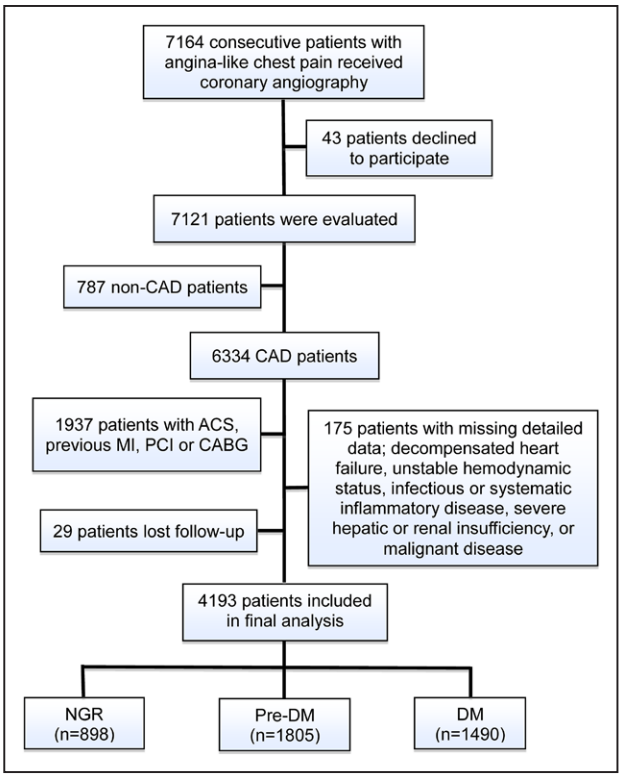

Figure 1. Flowchart illustrating study population. ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM, diabetes mellitus; NGR, normal glucose regulation; and PCI, percutaneous coronary intervention.

Statistical Analysis

Continuous variables are expressed as mean±standard deviation (SD) or median with interquartile range as appropriate, and differences between groups were determined using the student's *t* test, analysis of variance, or nonparametric test where appropriate. Categorical variables were presented as number (percentage) and analyzed by chi-squared statistic test or fisher exact test. Linear regression was used to estimate the independent predictors for coronary severity as measured by Gensini score (GS). The event-free survival rates among subgroups according to DM status or both DM and hypertension status were estimated by the Kaplan–Meier method and compared by the log-rank test. Cox proportional hazard models were performed to calculate hazard ratios (HRs) for CVD events of participants with pre-DM or DM compared with those with NGR. HRs for CVD events were also computed for participants with pre-DM or DM, with or without the presence of hypertension, compared with participants with normal blood glucose and normal BP. The analyses were initially performed adjusting for age and sex in model 1 and model 4; further adjustments were subsequently made for current smoking, hypertension, GS, left ventricular ejection fraction, triglyceride, low-density lipoprotein cholesterol, and erythrocyte sedimentation rate

(ESR) in model 5. Models 2 and 3 adjusted all the factors in model 5 plus hypertension defined by the JNC-7 and 2017 ACC/AHA criteria, respectively.

The statistical analysis was performed with SPSS version 20.0 software (SPSS Inc., Chicago, IL). In chi-squared statistic test, for comparisons between any 2 of the 3 groups according to DM status, 2-tailed P values <0.017 were considered statistically significant, while for comparisons between any 2 of the 6 groups according to DM and hypertension status, 2-tailed P values <0.003 were considered statistically significant. Two-tailed P values <0.05 were considered to be statistically significant in all the rest of the analyses.

Results

Baseline Characteristics

Among the subjects, 43.0% were defined as pre-DM, 35.5% had DM, and the rest 21.5% had NGR (Figure 1). The baseline demographics and clinical characteristics of the study population are shown in Table 1, both overall and according to DM status (NGR group, pre-DM group, and DM group). The prevalence of hypertension defined according to the JNC-7 criteria in NGR, pre-DM, and DM was 56.7%, 59.9%, and 71.6%, respectively. Meanwhile, the prevalence of hypertension diagnosed by the 2017 ACC/AHA guideline was 79.7%, 80.8%, and 88.1% in the 3 groups. The DM population had a significantly higher incidence of hypertension compared with the NGR or pre-DM individuals. The age, fasting plasma glucose, HbA1c, triglyceride, high-sensitivity C-reactive protein, fibrinogen, and ESR were positively associated with the DM status from NGR to DM (all P<0.001). Participants in the NGR group were more likely to be males (P<0.001) and smokers (P=0.008) compared with those of the other 2 groups. Meanwhile, individuals with DM had higher body mass index and systolic BP (P<0.001, respectively) and lower left ventricular ejection fraction (P=0.023) and high-density lipoprotein cholesterol levels (P<0.001) than participants with pre-DM or NGR. Moreover, pre-DM group had significantly higher total cholesterol and low-density lipoprotein cholesterol levels than the NGR group and higher lipoprotein (a) levels compared with the other 2 groups (all P<0.05). The prescribed medications were similar among the 3 groups (all P>0.05).

Pre-DM and Coronary Severity

The coronary severity was assessed in different subgroups according to DM status. As shown in Figure 2A and 2B, DM group had significantly higher log-transformed GS and more patients with multivessel disease than in any other group (all P<0.001). However, there was no significant difference of log-transformed GS and the proportion of multivessel disease between pre-DM and NGR groups (both P>0.05). Meanwhile, using multivariate linear regression analysis adjusting for sex, age, body mass index, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, ESR and hypertension, only DM group was independently associated with GS compared with NGR group (P<0.001). Because of the high prevalence of hypertension in our population, especially according to the 2017 ACC/AHA criteria, we further evaluated the association of 3 subgroups based on DM status (NGR, pre-DM, and DM), with the coronary severity stratified according to the presence or absence of hypertension [NGR/−hypertension (HTN) as reference, pre-DM/−HTN, DM/−HTN, NGR/+HTN, pre-DM/+HTN, and DM/+HTN]. When the hypertension was defined according to the JNC-7 criteria, compared with the reference group (NGR/−HTN group), all the other groups (P<0.01, respectively) excepting the pre-DM/-HTN group (P>0.05) had significantly higher log-transformed GS and more patients with multivessel disease (Figure 2C and 2D). Furthermore, the results were similar when the hypertension was diagnosed by the 2017 ACC/AHA criteria (data not shown). After adjusting for sex, age, body mass index, smoking, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, creatinine, and ESR in multivariate linear regression analysis, DM/−HTN, NGR/+HTN, pre-DM/+HTN, and DM/+HTN group still had a positive association with GS compared with the reference group (all P<0.05).

Pre-DM and CVD End Points

Over an average of 11 338 patient-years follow-up, 434 end point events were recorded (46 died, 39 suffered nonfatal myocardial infarction, 84 had strokes, 176 underwent unplanned revascularization procedures, and 89 had hospitalized unstable angina). Patients who suffered acute coronary syndrome and underwent revascularization procedures were assigned once in the analysis. The corresponding incidence rates of CVD events in NGR, pre-DM, and DM group were 7.8%, 9.8%, and 12.6%, respectively. Kaplan–Meier analysis with log-rank test (Figure 3A) showed that participants with DM had the lowest cumulative event-free survival rate among the 3 groups (P<0.05 for all comparisons), whereas there was no significant difference between pre-DM and NGR groups (P>0.05). When the participants were categorized according to both DM and hypertension status (Figure 3B and 3C), DM/−HTN, pre-DM/+HTN, and DM/+HTN groups had significantly lower cumulative event-free survival rates compared with the reference group (NGR/−HTN group) with the 2 guideline definitions of hypertension (all P<0.05).

The adjusted HRs and 95% confidence interval (CI) of CVD end point events according to the DM status are shown in Table 2. A baseline DM had a 1.59× higher risk of CVD events occurrence in the crude model compared with the reference NGR group. Additional adjustment for multivariable in 3 models only slightly attenuated this association, and DM was still significantly and independently associated with CVD events risk. However, pre-DM did not increase CVD events risk significantly compared with the reference group in any adjusted model. Furthermore, adjusted Cox models were fitted with different DM status in normotensive and hypertensive participants in Table 3, with hypertension defined according to 2 criteria. In the JNC-7 criteria, after adjusting for potential confounding factors in Cox models, compared with the reference group (NGR/−HTN group), pre-DM alone, isolated DM, or hypertension alone was not associated with elevated CVD events risk (P>0.05, all). However, pre-DM combined with hypertension did significantly increase the risk for developing CVD events when compared with the reference group, with adjusted HR of 1.58 (95% CI, 1.01–2.46). Moreover, coexistence of DM and hypertension was related to the most significant increase of the risk of CVD events compared with participants with normal plasma glucose and normal BP (HR, 1.69; 95% CI, 1.09–2.63).

Table 1. Characteristics of the Study Participants According to DM Status at Baseline

Variable	DM Status				*P* Value
	Overall (n=4193)	NGR (n=898)	Pre-DM (n=1805)	DM (n=1490)	
Age, y	57.7±10.0	54.6±10.5	58.2±9.6	58.9±9.7	<0.001
Male, %	71.8	77.7	70.9	69.3	<0.001
Hypertension,* %	63.4	56.7	59.9	71.6	<0.001
Hypertension,† %	83.1	79.7	80.8	88.1	<0.001
Current smokers, %	42.9	46.8	43.2	40.2	0.008
BMI, kg/m^2	25.83±3.14	25.41±3.12	25.63±3.12	26.32±3.11	<0.001
SBP, mm Hg	126.8±17.0	125.2±16.9	126.0±16.9	128.8±17.0	<0.001
DBP, mm Hg	77.7±10.8	78.1±11.3	77.4±10.7	77.9±10.7	0.218
LVEF, %	64.7±6.7	64.8±6.6	64.9±6.5	64.3±6.9	0.023
FPG, mmol/L	5.80±1.72	4.77±0.41	5.21±0.59	7.13±2.23	<0.001
HbA1c, %	6.34±1.12	5.38±0.22	5.94±0.25	7.39±1.26	<0.001
TC, mmol/L	4.19±1.15	4.08±1.10	4.26±1.15	4.18±1.16	0.001
HDL-C, mmol/L	1.06±0.29	1.06±0.31	1.08±0.29	1.02±0.27	<0.001
LDL-C, mmol/L	2.55±0.99	2.48±1.04	2.60±0.94	2.53±1.03	0.014
TG, mmol/L	1.51 (1.12–2.13)	1.40 (1.02–1.99)	1.52 (1.12–2.12)	1.58 (1.19–2.25)	<0.001
Lp(a), mg/L	149.86 (66.67–358.65)	149.15 (68.63–361.37)	163.40 (70.43–384.20)	139.07 (61.60–330.16)	0.007
Creatinine, μmol/L	76.86±15.66	78.11±15.57	76.52±14.79	76.51±16.67	0.026
HsCRP, mg/L	1.45 (0.76–2.98)	1.17 (0.65–2.36)	1.44 (0.77–3.01)	1.65 (0.84–3.49)	<0.001
Fibrinogen, g/L	3.24±0.78	3.06±0.73	3.25±0.77	3.34±0.80	<0.001
ESR, mm/h	7 (3–14)	6 (2–11)	7 (3–13)	8 (4–16)	<0.001
Medications					
Aspirin, %	83.7	82.5	84.6	83.1	0.465
Statins, %	9.7	8.4	10.4	9.7	0.267
ACEI/ARB, %	22.1	19.1	22.5	23.4	0.155
β-Blockers, %	45.1	43.4	16.3	44.7	0.514
CCB, %	19.2	18.9	18.6	20.0	0.710

Continuous values are summarized as mean±SD, median (interquartile range) and categorical variables as percentage. ACC/AHA indicates American College of Cardiology/American Heart Association; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CCB, calcium channel blockers; DBP, diastolic blood pressure; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HsCRP, high-sensitivity C-reactive protein; JNC-7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); LVEF, left ventricular ejection fraction; SBP, systolic blood pressure; TC, total cholesterol; and TG, triglyceride.

*Hypertension defined by the JNC-7 criteria.

†Hypertension diagnosed according to the 2017 ACC/AHA guideline.

When hypertension was diagnosed by the 2017 ACC/AHA guideline, the results were consistent with the JNC-7 criteria except that DM alone was also significantly associated with the CVD events risk (HR, 2.47; 95% CI, 1.03–5.95), and that the CVD events risk of coexistence of hypertension and pre-DM or DM was relatively higher (HR, 2.37; 95% CI, 1.11–5.07; HR, 2.85; 95% CI, 1.33–6.09; respectively).

Discussion

In this prospective study on new-onset CAD patients undergoing coronary angiography, we, interestingly, found that pre-DM was not associated with an increased CVD risk and had a similar risk with subjects with NGR. However, when it occurred in the hypertensive subjects defined by either JNC-7 or 2017 ACC/AHA criteria, the risk for more severe coronary lesions was significantly elevated compared with that for participants with normal plasma glucose and normal BP. Meanwhile, under the diagnostic criteria of JNC-7, the risk for CVD events of pre-DM combined with hypertension was increased by 1.58-fold compared with normoglycemic and normotensive participants. Moreover, when hypertension was diagnosed according to the 2017 ACC/AHA criteria, the risk of pre-DM plus hypertension for CVD events was significantly increased by 2.37-fold. Our results may provide new information and evidence for the relation of pre-DM status to severity and clinical prognosis of patients with stable, new-onset CAD.

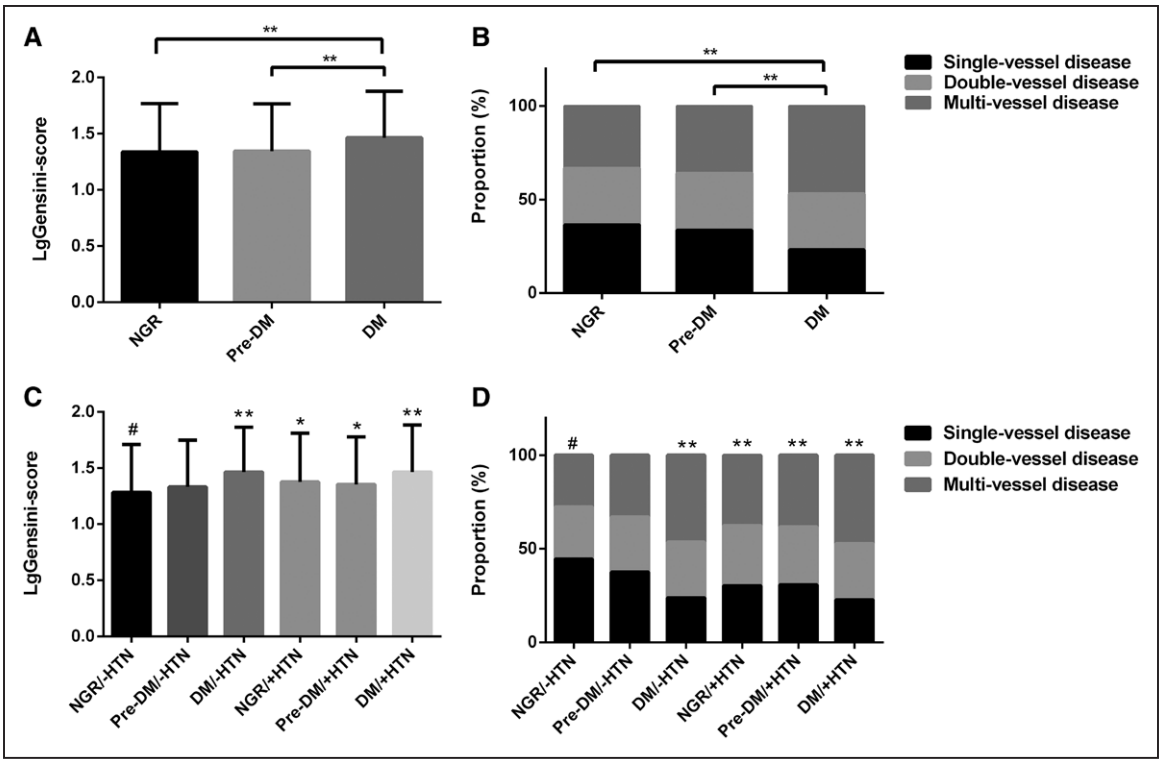

Figure 2. Coronary severity according to DM or both DM and HTN status. **A**, Log-transformed Gensini score according to DM status; **B**, Coronary lesion vessels according to DM status; **C**, Log-transformed Gensini score according to DM and HTN status; **D**, Coronary lesion vessels according to DM and HTN status. DM indicates diabetes mellitus; HTN, hypertension; and NGR, normal glucose regulation. #Reference group; *P<0.01; **P<0.001.

DM is a most important and common metabolic disease with an increasing morbidity worldwide.[8] It represents a public health problem of epidemic proportions in both developed and developing countries.[14] What's more, it is well determined that DM increases morbidity and mortality of CAD, which is the leading cause of death worldwide.[9] The most important risk factor for DM is a condition called pre-DM, which is generally defined as IFG, impaired glucose tolerance, or both. Later, elevated HbA1c, which integrates plasma glucose over time, is promoted as another indicator of pre-DM.[1] The predisposition of pre-DM to DM makes it a potential risk factor for CVD as well.[8] The prevalence of pre-DM in the United States had increased to an estimated rate of 36.2% in 2010.[3] Meanwhile, as noted in a report in 2017 by Wang et al,[4] ≈35.7% of the adults had pre-DM in China, and the incidence rate was as high as 50.1% in another report.[15] Because of the high and widespread prevalence of pre-DM, an ongoing debate is whether pre-DM is an independent risk factor of CVD and whether it deserves targeted identification and clinical intervention. Several studies indicated that dysglycemia within nondiabetic glucose range was associated with increased risk for CVD.[5,16–18] However, recently, a systematic review[10] and 3 meta-analysis[10,19] showed that pre-DM were only associated with a modest increase in the risk for CVD. Moreover, the first wave of the Nord-Trondelag Health Study concluded that DM, but not hyperglycemia below the current diagnostic threshold for DM, had a significantly higher risk for fatal CAD in both genders.[9] Another large cohort study in Korea reported that the increased risk for myocardial infarction could not be observed in the IFG population and only be observed in the diabetic glucose level.[20] Furthermore, Liu et al[7] and Qiu et al[6] indicated that pre-DM per se did not increase the CVD risk and was associated with it only when combined with other metabolic disorders. In our study, pre-DM was defined by an elevation of fasting plasma glucose, 2-hour glucose, or HbA1c levels. We also did not find an association between pre-DM alone and the severity and outcomes of stable, new-onset CAD, which provide more evidence for the lack of correlation between pre-DM and CVD risk.

Hypertension is another significant metabolic disease with powerful risk for CVD and is present in up to two-thirds of DM patients.[21] It has much in common with DM, such as caused by unhealthy lifestyles associated with insulin resistance and leading to similar complications.[22] Similarly, pre-DM also aggregates commonly with other CVD risk factors.[8] In this study, the prevalence of hypertension defined according to the JNC-7 criteria in NGR, pre-DM, and DM was 56.7%, 59.9%, and 71.6%, respectively. Meanwhile, when diagnosed by the 2017 ACC/AHA guideline, it was 79.7%, 80.8%, and 88.1% in the 3 groups, respectively. The population with DM had a significantly higher prevalence of hypertension than other 2 groups, while the difference between pre-DM and NGR group was not significant. The relative higher coexistence of DM and hypertension compared with previous studies and the small difference of the prevalence of hypertension between subjects with pre-DM and NGR may both be ascribed to our CAD population, which is different from the general population. Meanwhile, close to 20% patients in our study population had newly diagnosed hypertension according to the 2017 ACC/AHA guideline, which was higher than the 13.7% reported in the guideline. The reason may be that patients with CAD have higher BP than the general population. What's

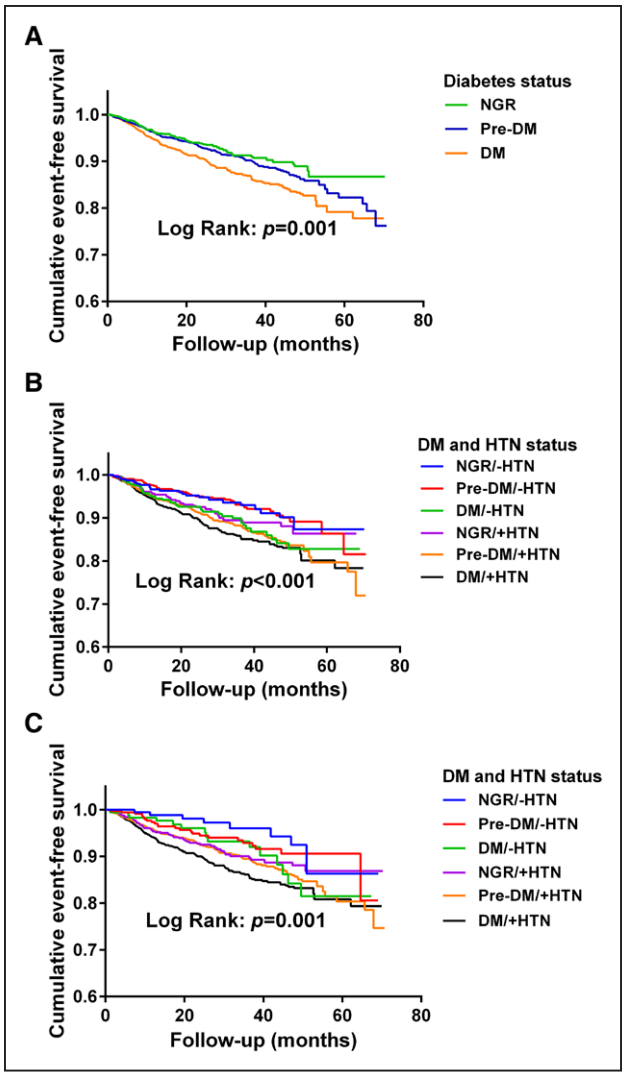

Figure 3. The cumulative event-free survival analysis according to (**A**) DM status, (**B**) DM and HTN status, with HTN defined according to the JNC-7 criteria, and (**C**) DM and HTN status, with HTN defined according to the 2017 ACC/AHA guideline. DM indicates diabetes mellitus; HTN, hypertension; JNC-7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; and NGR, normal glucose regulation.

more, it has been well demonstrated that the coexistence of DM and hypertension certainly increased the risk of CVD and other complications, regardless of the country.[22] However, studies on whether pre-DM carries any additional CVD risk in patients with hypertension, or acts as an additional CVD risk independently of hypertension are insufficient and rare. Qiu et al[6] demonstrated that pre-DM, only when associated with hypertension, would significantly elevate CVD risk. Zhang et al[11] found that there was no difference in the rate of incident CVD among normotensive participants with NGR, IFG, or impaired glucose tolerance, while IFG or impaired glucose tolerance plus prehypertension greatly increased the CVD risk. Up to now, there have been no studies to affirm the effects of hypertension on the association between pre-DM and CVD risk, including coronary severity and clinical outcomes in patients with stable, new-onset CAD. The current analysis indicated that compared with participants with NGR and normal BP, those with pre-DM alone had no significant increase of risk for coronary severity and CVD events, while pre-DM plus hypertension significantly elevated CVD risk. The results not only enhance our understanding of the role of pre-DM in the CAD population but also provide guidance for future prevention and treatment of patients with CAD. In addition, hypertension, as is well established, increased coronary severity significantly either alone or concurrent with pre-DM. Hypertension alone also had a higher HR for CVD events than pre-DM alone, though not reaching a statistical significance. Therefore, among patients with pre-DM and hypertension, clinicians may need to focus more on tight BP control.

Why does pre-DM combined with hypertension but not pre-DM alone increase the cardiovascular risk? To the best of our knowledge, hypertension damages endothelial function through hemodynamic changes, leading to endothelial dysfunction,[21,23,24] increased oxidative stress[24] and serum levels of inflammatory factors, such as IL-6 (interleukin-6) and TNF-α (tumor necrosis factor-α), and upregulated expression of adhesion molecules, such as ICAM-1 (intercellular adhesion molecule-1) and P-selectin.[23] These effects are the key initiator for arteriosclerosis, thrombosis, and their complications.[21,23] Besides hypertension, dysglycemia is the second most common risk factor for endothelial dysfunction, oxidative stress, and inflammation.[23] Thus, high BP and IGR have similar mechanisms to increase CVD risk, and it seems to be reasonable that pre-DM and hypertension together would have higher risk for CVD than either one alone. Moreover, it has been demonstrated by Huang et al[23] that patients with both hypertension and pre-DM showed significantly higher levels of ICAM-1 and TNF-α compared with the subjects with hypertension alone, suggesting that the comorbidity of these diseases may aggravate endothelial dysfunction and inflammation by promoting the expression of ICAM-1 and TNF-α and, thus, increase the CVD risk. In this study, we compared inflammation markers including high-sensitivity C-reactive protein, fibrinogen, and ESR between different categories according to DM status or both DM and hypertension status. It is not surprising that pre-DM combined with hypertension had significantly higher high-sensitivity C-reactive protein, fibrinogen, and ESR than pre-DM alone or hypertension alone (data not shown), which lend support to the above explanation. In short, the coexistence of hypertension and DM or pre-DM may combine to multiply the risk of inciting endothelial damage and then increase the risk for adverse CVD events through multiple mechanisms, which need more studies to further clarify in future.

As for the strengths, our study is the first studying the impact of hypertension on the association between pre-DM and CVD risk, including coronary severity and clinical outcomes in patients with angiography-proven stable, new-onset CAD. Moreover, our participants were from a homogeneous population and had no intervention during the visit, which would be good enough to reflect human's natural development of disease. Last but not least, considering the recent publication of 2017 ACC/AHA guideline, we added the new definition criterion of hypertension into our analysis.

However, our study is limited by several facts: first, as inherent to the nature of any observational and prospective study, our

Table 2. Cox Regression Models in Predicting Cardiovascular Events According to DM Status at Baseline

Category (n, Events/Subjects)	Hazards Ratio (95% CI)			
	Unadjusted Model	Model 1	Model 2	Model 3
NGR* (70/898)	1.00	1.00	1.00	1.00
Pre-DM (177/1805)	1.20 (0.91–1.59)	1.15 (0.86–1.52)	1.16 (0.87–1.56)	1.17 (0.87–1.56)
DM (187/1490)	1.59(1.20–2.01)†	1.49(1.13–1.98)†	1.42(1.06–1.90)‡	1.43(1.07–1.91)‡

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, current smoking, hypertension, Gensini score, left ventricular ejection fraction, triglyceride, low-density lipoprotein cholesterol, and erythrocyte sedimentation rate; Model 3 adjusted for hypertension defined by the 2017 ACC/AHA criteria and other risk factors in the model 2. ACC/AHA indicates American College of Cardiology/American Heart Association; CI, confidence interval; DM, diabetes mellitus; and NGR, normal glucose regulation.

*Reference group.

†$P<0.01$.

‡$P<0.05$.

findings are subject to confounding factors and also the level of risk factors at baseline examination might change during the follow up. Second, the follow-up time and sample size in this study needed to be longer and larger to examine the prognostic value of pre-DM alone or plus hypertension in the long-term outcomes. Third, this is a study in Chinese patients with established CAD, which may limit the generalizability of our findings. However, it is likely applicable to the many populations in China and around the world because of the high incidence of CAD.

Perspectives

CVD is still one of the most common chronic diseases worldwide with a high morbidity and mortality. Currently, whether pre-DM is an independent risk factor for CVD and requires intervention is a hot topic. Perhaps, pre-DM alone cannot predict CVD prognosis, and its adverse effect on CVD only exists when combined with hypertension (defined by the JNC-7 or 2017AHA/ACC criteria) or other metabolic problems. For CAD patients with pre-DM and normal BP, pharmacological intervention may not be appropriate, and moderate lifestyle modification and regular monitoring are recommended. Special attention should be paid to CAD population with both pre-DM and hypertension. Besides lifestyle modification, drug treatment for blood glucose and BP control may be indicated for the prevention of CVD events. Although this is a relatively short-term study, longer-term follow-up of this population will lead to better understanding of the effects of pre-DM alone or plus hypertension on CVD outcomes. Moreover, a prospective randomized control trial with a large sample size and long-term follow-up is urgently needed to further confirm our findings.

Table 3. Cox Regression Models in Predicting Cardiovascular Events According to Diabetic Status and Hypertension at Baseline

Category (n, Events/Subjects)	Hazard Ratio (95% CI)		
	Unadjusted Model	Model 4	Model 5
JNC-7 criteria			
NGR/−HTN* (25/389)	1.00	1.00	1.00
Pre-DM/−HTN (52/723)	1.02 (0.63–1.66)	0.98 (0.61–1.59)	0.94 (0.57–1.55)
DM/−HTN (48/423)	1.77 (1.09–2.88)†	1.71 (1.05–2.78)†	1.62 (0.99–2.66)
NGR/+HTN (45/509)	1.37 (0.84–2.25)	1.35 (0.82–2.21)	1.23 (0.74–2.04)
Pre-DM/+HTN (125/1082)	1.75 (1.14–2.69)†	1.64 (1.06–2.53)†	1.58 (1.01–2.46)†
DM/+HTN (139/1067)	1.97 (1.29–3.02)‡	1.83 (1.19–2.81)‡	1.69 (1.09–2.63)†
2017 ACC/AHA criteria			
NGR/−HTN* (8/182)	1.00	1.00	1.00
Pre-DM/−HTN (26/347)	1.56 (0.70–3.47)	1.49 (0.67–3.33)	1.68 (0.72–3.90)
DM/−HTN (19/178)	2.45 (1.07–5.64)†	2.31 (1.01–5.33)†	2.47 (1.03–5.95)†
NGR/+HTN (62/716)	2.08 (0.99–4.35)	2.04 (0.98–4.27)	2.15 (0.98–4.71)
Pre-DM/+HTN (151/1458)	2.38 (1.17–4.85)†	2.23 (1.09–4.56)†	2.37 (1.11–5.07)†
DM/+HTN (168/1312)	2.99 (1.47–6.08)‡	2.78 (1.36–5.66)‡	2.85 (1.33–6.09)‡

Model 4 adjusted for age and sex; model 5 adjusted for age, sex, current smoking, Gensini score, left ventricular ejection fraction, triglyceride, low-density lipoprotein cholesterol, and erythrocyte sedimentation rate. DM, diabetes mellitus; HTN, hypertension; JNC-7, Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; NGR, normal glucose regulation.

*Reference group.

†$P<0.05$.

‡$P<0.01$.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Whether prediabetes mellitus alone or combined with other metabolic diseases, such as hypertension, is an independent predictor for cardiovascular risk has not been fully clarified.
- Moreover, relative studies have still been scarce, especially in patients with established stable coronary artery disease.
- Our study is the first to explore the impact of hypertension on the association between prediabetes mellitus and cardiovascular risk, including coronary severity and cardiovascular outcomes in patients with angiography-proven stable, new-onset coronary artery disease.

What Is Relevant?

- Prediabetes mellitus with or without hypertension showed different effects on coronary severity and cardiovascular outcomes, suggesting that prediabetes mellitus alone might not be an independent risk factor for cardiovascular disease.

Summary

This study provides strong evidence that among patients with stable, new-onset coronary artery disease, the increased cardiovascular risk with prediabetes mellitus is largely driven by the coexistence of hypertension rather than prediabetes per se. Our results suggest that in patients with coronary artery disease combined with both prediabetes and hypertension, their blood glucose and blood pressure need intensive management.