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Atherogenic dyslipidemia and prognosis in coronary artery disease patients with pre-diabetes and diabetes

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Title: Atherogenic dyslipidemia and prognosis in coronary artery disease patients with pre-diabetes and diabetes

Running Title: lipid, glucose and outcomes

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Abstract

Objective: The aim of the study is to investigate the impacts of triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) dyslipidemia on prognosis in coronary artery disease patients with different glucose metabolism status.

Design: An observational cohort study

Setting/Participants: A total of 3057 patients with stable coronary artery disease (CAD) were consecutively enrolled and divided into 3 groups according to different glucose metabolism

p presented 1.441-fold higher risk of CVEs (HR:1.44, 95%CI: 1.02-2.04). Wstatus [diabetes mellitus (DM), pre-diabetes mellitus (Pre-DM), normal glycaemia regulation (NGR)]. Atherogenic dyslipidemia (AD) was defined as TG≥1.7mmol/L and HDL-C<1.0mmol/L for man or <1.3mmol/L for women. These patients were further classified into 6 subgroups by status of atherogenic dyslipidemia. All subjects were followed up for the cardiovascular events (CVEs).

Primary outcome measure: The primary endpoints (CVEs) were cardiovascular mortality, non-fatal myocardial infarction (MI) and stroke.

Results: During a median follow-up of 6.1 years, 308 (10.1%) CVEs occurred. No significant difference in occurrence of CVEs was observed between NGR and Pre-DM groups [Hazard Ratio (HR): 1.252, 95% confidence interval (CI): 0.89-1.76] while DM grouhen the participants were categorized according to combined status of two parameters, the cardiovascular risk was significantly elevated in Pre-DM or DM plus AD group compared with the NGR plus Non-AD group (HR: 1.62, 95%CI: 1.06-2.46 and HR: 1.81, 95%CI: 1.13-2.91).

Conclusions: The present study firstly showed that the presence of atherogenic dyslipidemia had a significant impact on CVEs in Pre-DM.

Keywords: triglyceride, HDL-C, pre-diabetes, prognosis

Strengths and limitations of this study

- This study firstly indicated that the presence of atherogenic dyslipidemia had a significant impact on cardiovascular outcome in patients with pre-diabetes mellitus (Pre-DM)
- In the current study, hard endpoints containing nonfatal strokes, nonfatal myocardial infarction, and cardiovascular mortality were observed during a relatively long follow-up period.
- The levels of triglyceride and high-density lipoprotein cholesterol were measured only at the baseline.
- We did not assess the all metabolic factors and parameters about insulin resistance due to the features of patients in our study.

Introduction

Dyslipidemia is one of the key drivers in atherogenesis. Lipid lowering therapy targeting at low density lipoprotein cholesterol (LDL-C) has been proved to be efficient in decreasing the progression of arteriosclerotic cardiovascular disease (ASCVD) [1]. Moreover, strong evidence in epidemiological, genetic and prospective cohort studies verifies that high triglyceride (TG) and/or low levels of high density lipoprotein cholesterol (HDL-C) are associated with cardiovascular disease（CVD）risk [2-4]. It has been demonstrated in large-scale, randomized, clinical trials that appropriate treatment of hypertriglyceridemia produces a reduction in cardiovascular events (CVEs) [5]. However, clinical trials about therapeutic interventions towards low HDL-C provided fewer convincing results. Anacetrapib reduced CVEs by 9% in the Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) study but it was not clear whether the risk reduction was attributed to the increase in HDL-C [6].

Type 2 diabetes mellitus (T2DM) is also one of the main risk factors of CVD and with lipid profiles that are characterized as high TG accompanied by low HDL-C [7]. Previous studies indicated that individuals with atherogenic dyslipidemia (AD) presented higher risk of CVD in DM patients [8]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with a combination of high baseline TG (≥204 mg/dL, highest tertile and a low baseline HDL-C (≤34 mg/dL, lowest tertile) showed possible benefit from fenofibrate plus simvastatin therapy [9]. Standards of medical care in diabetes from American Diabetes Association (ADA) also recommended intensify lifestyle therapy and optimize glycemic control for patients with elevated TG levels and/or low HDL cholesterol [10].

Pre-diabetes (Pre-DM) is an abnormal glucose regulation status with high predisposition to developing T2DM [11]. Pre-DM subjects had similar lipid profile as DM [12]. However, the prognosis of Pre-DM patients with coronary artery disease (CAD) has less been examined. Also, whether the Pre-DM alone or accompanied by AD can increase CVD risk in patients with CAD is lacking. The aim of the study is to test the hypothesis that Pre-DM plu sAD had a significant impact on cardiovascular outcomes in patients with angiography-proven CAD.

Materials and Methods

Study Design and Participants

Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Informed written consents were obtained from all patients enrolled in this study.

As described in the flowchart (Fig. 1), from March 2011 to November 2013, 4249 consecutive patients scheduled for coronary angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically suspected CAD was evaluated for the study**.** Among these patients, 382 were excluded because they are not angiography-proven CAD (coronary stenosis ≥50% of at least one coronary artery). Other patients were excluded for following reasons: acute coronary syndrome (ACS), previous percutaneous coronary coronary artery intervention (PCI) and bypass grafting (CABG), heart failure, severe liver and/or renal insufficiency, thyroid dysfunction, systematic inflammatory disease, malignant disease, and excessive drinking. Patients were followed up at 6 months' intervals by means of interviewing directly or using telephone. Trained nurses or physicians who were blinded to the clinical data fulfilled the interview. The primary endpoints (CVEs) were cardiovascular mortality, non-fatal myocardial infarction (MI) and stroke. Non-fatal myocardial infarction was diagnosed as

positive cardiac troponins along with typical chest pain or typical electrocardiogram serial changes. Stroke was diagnosed by the presence of typical symptoms and imaging.

DM was diagnosed by fasting plasma glucose (FPG) ≥7.0 mmol/L or the 2-h plasma glucose of the oral glucose tolerance test ≥11.1mmol/L or currently using hypoglycaemic drugs or insulin. Pre-DM was diagnosed when participants who had no self-reported DM but met the diagnostic criteria of Pre-DM [13]. Patients who were without DM or Pre-DM were defined as normal glucose regulation (NGR). Atherogenic dyslipidemia (AD) was defined as TG≥1.7mmol/L and HDL-C<1.0mmol/L for man or <1.3mmol/L for women. Hypertension was defined as a self-reported hypertension, currently taking antihypertensive drugs or recorded systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg for three or more consecutive times. Information of other disease, family history, and prior therapy of every patient was collected from self-reported medical history.

Laboratory Analysis

Blood samples were obtained from each patient from the cubital vein after at least 12-h fasting. Concentrations of total cholesterol (TC), TG, LDL-C, HDL-C were measured using automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) in an enzymatic assay. The concentrations of glucose were measured by enzymatic hexokinase method. HbA1c was measured using Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan).

Evaluation of Coronary Severity

Angiographic data were evaluated from catheter laboratory records by 3 experienced interventional cardiologists according to our previous studies [14]. The Gensini score (GS) was calculated as previously described [15].

Statistical Analysis

The values were expressed as the mean±SD or median (Q1–Q3 quartiles) for the continuous variables and the number (percentage) for the categorical variables. The Kolmogorov–Smirnov

test was used to test the distribution pattern. The differences of clinical characteristics between groups were analyzed using the student's t test, analysis of variance, or nonparametric test, chi-squared statistic test or fisher exact test where appropriate. The event-free survival rates among groups were estimated by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratios (HRs). A p-value <0.05 was considered statistically significant. The statistical analyses were performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Results

As presented in Fig. 1, among 3057 subjects, 20.0%, 44.8%, and 35.2.0% were diagnosed as NGR, Pre-DM, and DM respectively according to ADA criteria. The baseline characteristics of the study participants were shown in Table 1. The age, body mass index (BMI), glucose, HbA1c, TG, and high-sensitivity C-reactive protein (hsCRP) were positively associated with the status of glucose metabolism from NGR to DM (all P<0.001). The proportion of patients with hypertension was elevated from NGR to DM (p<0.001). Patients with Pre-DM and DM had higher levels of TC and LDL-C than the NGR group. Meanwhile, DM but not Pre-DM patients had significantly lower levels of HDL-C and left ventricle ejection fraction (LVEF) than NGR population. There was no significant difference regarding sex, smoking, drinking, family history of CAD, creatinine, and medication prescriptions among the three groups (p>0.05).

The coronary severity was compared among different status of glucose metabolism. As shown in Fig. 2a and 2b, DM group had significantly higher GS ($p<0.05$) while there was no significant difference between Pre-DM and NGR groups ($P>0.05$). We further divided the patients into the six groups according to status of glucose metabolism and AD (NGR plus Non-AD; Pre-DM plus Non-AD; DM plus Non-AD; NGR plusAD; Pre-DM, plus AD; DM plus AD). We set NGR and Non-AD group as reference and compared its GS with that of other groups. All the other groups had higher GS than the reference group (all $p<0.05$) except Pre-DM plus Non-AD and NGR plus AD group ($p>0.05$ respectively).

Over a median follow-up time of 6.1 years (5.1 to 7.5 years), 308 CVEs occurred (112 died, 73 suffered nonfatal MI, 123 had nonfatal strokes). The prevalence of CVEs in NGR, Pre-DM, and DM group was 7.5%, 9.9%, and 11.8%, respectively. Kaplan–Meier analysis (Fig. 3a) showed that DM subjects had the lowest event-free survival rate among the 3 groups ($p<0.05$) while there was no significant difference between that of Pre-DM and NGR groups ($p>0.05$)**.** However, when the patients were evaluated according to both glucose metabolism and AD status: DM plus Non-AD, Pre-DM plus AD, and DM plus AD groups had significantly lower cumulative event-free survival rates compared with the reference group (NGR plus Non-AD group, Fig. 3b, all $p<0.05$ respectively). As presented in Table 2, univariate Cox regression models showed that patients with DM had 1.441-fold higher risk of CVEs than NGR subjects [HR:1.441, 95% coincidence interval (CI):1.018-2.041, $p<0.05$]. Additional adjustment for other variables did not change the significance of association. The presence of Pre-DM did not show increase in CVEs risk when compared with NGR group ($p>0.05$). Moreover, multivariate Cox regression analyses according to both glucose metabolism and AD status indicated that patients in DM plus non-AD, Pre-DM plus AD, and DM plus AD groups had 1.62-fold (95%CI: 1.01-2.46), 1.73-fold (95%CI:1.08-2.76), and 1.81-fold (95%CI1.13-2.91) higher risk of CVEs (Table 3, all $p<0.05$ respectively).

Discussion

The causality of high TG and/or low HDL-C to ASCVD has been controversial during the past decades. Previous prospective studies have shown that patients with high TG combined with low HDL-C may be more likely to develop ASCVD, especially in those with DM [16]. In this study, we investigated the impact of AD on cardiovascular outcomes in stable, angiography-proven CAD patients in different glucose metabolism status. We found that patients with DM but not those with Pre-DM had more severe coronary stenosis and higher risk of CVEs when the patients were simply divided into the three groups: DM, Pre-DM, and NGR. Interestingly, when patients were categorized according to both status of glucose metabolism and AD, patient with Pre-DM plus AD had higher GS and 1615-fold increased risk of CVEs compared with that in subjects with NGR and Non-AD. Thus, our study, for the first time, suggested that the presence of Pre-DM had significant impact on cardiovascular outcomes when combined with AD.

High TG and low HDL-C are common lipid abnormalities among adult population, especially in Chinese subjects. According to DYSlipidemia International Study (DYSIS), 41.8% patients had high TG and 31.9% patients had low HDL-C among the Chinese population in primary prevention [17]. Additionally, studies about lowering TG and raising HDL-C on reducing CVD risk were with inconsistent results [6,9]. For example, fibrates did not associate with conclusive effect in ASCVD reduction in ACCORD trials while patients who received 2 g of icosapent ethyl twice daily had lower risk of ischemic events in Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [9,18]. However, in randomized controlled trials (RCTs), cholestery l ester transfer protein (CETP) inhibitors, which aimed at increasing plasma HDL-C, failed to reduce CVEs rates [9, 19-21]. In the meanwhile, Mendelian analysis involving about 20,000 MI individuals and 50,000 controls demonstrated that 1 SD increase in TG levels was associated with 54% increase risk

of MI [22]. In contrast, no such association was found for patients with low baseline levels of HDL-C [3]. Moreover, high TG and low HDL-C were often regarded as a whole and defined as AD or metabolic dyslipidemia in many studies. In the EPIC-Norfolk prospective population study, healthy men with AD had 61% higher risk of CAD than those with normal TG and HDL [23]. Of noted, patients with obesity, insulin resistance or other metabolic abnormalities had higher prevalence of high TG and/or low HDL-C [24].

DM was the most common metabolic disease in the 21st century and approximately 415 million adults were with T2DM worldwide [25]. Prevalence of total diagnosed and undiagnosed diabetes in China also reached 10.9% in 2013 [26]. What's more, CAD was a common comorbidity and increased mortality in patients with DM. According to previous studies, DM patients without angiography-proven CAD showed low risk of MI or CVEs (defined as death, cardiac death, and MI), but the DM and CAD combination further increased the risk of ischemic stroke [27-28]. In our previous studies, among patients with established CAD, individuals with DM were associated with significantly higher risk of worse prognosis when they were combined with other CAD risk factors, including hypertension and Lp(a)-hyperlipoproteinemia [14, 29]. Therefore, in the present study, among patients with stable CAD, identifying whether AD is a risk factor for worse prognosis might be crucial.

In strong heart study, high TG plus low HDL levels were associated with a 1.54-fold greater occurrence risk for CAD and a 2.13-fold occurrence risk for stroke in community based African Americans with DM [8]. In a large cohort of 28,318 DM subjects, increased CAD risk was observed in both men and women with AD [16]. In the ACCORD trial, for participants with DM, fenofibrate plus simvastatin 40mg exhibited a 31% reduction in CVEs in the subgroup with baseline high TG and low HDL-C [9]. Other studies, such as Pemafibrate to Reduce Cardiovascular Outcomes by Reducing Triglycerides in Patients with Diabetes

(PROMINENT) study, also provided evidence about the risk of high TG and/or low HDL-C in DM patients [30].

In fact, more attention has recently been paid to the prevention of DM and the clinical characters in the early phase of impaired glucose metabolism. Pre-DM was an intermediate state between NGR and DM and with high predisposition to develop DM. This metabolic condition was often reversible. The rate of individuals with Pre-DM was almost three times higher than DM worldwide and in China (35.7% vs.10.9% in China) [25,31]. The prevalence of Pre-DM and CVEs risk have long been debating. Despite the differences of cut-off point in diagnose of pre-DM, studies and meta-analysis using blood glucose and HbA1c according to 2003 ADA guideline also had different results [32-33]. In our study population, as previously reported, the predictive value of Pre-DM for CVEs was less significant, which was also consistent with studies conducted by Liu et al and Qiu et al [19]. In the present study, 21.8%, 26.6% and 31.2% of patients had AD in NGR, Pre-DM and DM groups. Both Pre-DM and DM groups had higher rate of AD than NGR group. As the main findings of our study, stable CAD patients with Pre-DM plus AD had higher GS and increased risk of CVEs while no statistically significant difference were observed between Pre-DM alone and NGR plus Non-AD groups. Therefore, similar attention should be given to patients with Pre-DM and DM when they were with AD.

The present study had several virtues compared with previous published reports. Very few studies have evaluated the differences of coronary severity and outcomes according to both status of glucose metabolism and AD, especially in those with stable CAD. In addition, previous studies were also limited by the fact that the risk of high TG and/ or low HDL-C levels were analyzed separately within DM or NGR population, neglecting of the potential high risk which was caused by the interaction of lipid and glucose. Moreover, there were no such studies about the impacts of AD on cardiovascular outcomes in CAD patients with Pre-DM.

Apparently, a large sample size of angiography-proven CAD patients with high prevalence of DM and pre-DM were enrolled in the present study. Hard endpoints containing nonfatal strokes, nonfatal MI, and cardiovascular mortality were also observed during a relatively long follow-up period. Thereby, our study provided important information regarding dyslipidemia, pre-DM and outcome, which may influence our treatment decision for CAD patients with pre-DM.

Nevertheless, there are still several limitations in the present study. Firstly, this is a single center study among Chinses patients with stable CAD. Secondly, we measured triglyceride and HDL-C only at the baseline, the follow-up levels of TG/HDL-C may also be clinically significant. Thirdly, we did not assess the all metabolic factors and parameters about insulin resistance due to the features of patients in our study.

In conclusion, in our large sample size with long-term follow-up study, data, for the first time, indicated that the Pre-DM patients with AD had a significant impact on CVEs suggesting that the AD control in Pre-DM may also be a target for improving clinical outcomes.

Contributors

YG and J-LJ analyzed the data and drafted the manuscript. J-JL planned and designed the study. The rest of the authors were involved in collecting and researching data, reviewing and editing manuscript. All authors read and approved the final manuscript.

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Competing interests

None declared

Patient consent

Obtained.

Ethics approval

The study was performed according to the Declaration of Helsinki, and the hospital ethics review board (Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China) approved the protocol.

Data sharing statement

The technical appendix, statistical code and data set are available from the corresponding author.

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Figure Legends

Figure 1 Flowchart of the study

Figure 2 Coronary severity in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia * for $p<0.05$

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

Tables

Table 1. Baseline characteristics of the participants according to different glucose metabolism

	Total n=3057	NGR n=610	Pre-DM n=1370	DM n=1077	P
Clinical factors					
Age, years	58.5±9.8	55.5±10.0	58.8±9.4	59.9±9.8	<0.001
Male, n (%)	2149(70.3)	438(71.8)	956(69.8)	755(70.1)	0.651
BMI (kg/m^2)	25.6±3.2	25.0±3.0	25.5±3.2	26.1±3.2	<0.001
HT, n (%)	1904(62.3)	339(55.6)	804(58.7)	761(70.7)	<0.001
Family history of CAD	494(16.2)	112(18.4)	221(16.1)	161(14.9)	0.188
Current Smoker, n (%)	1580(51.7)	307(50.3)	714(52.1)	559(51.7)	0.751
Drinking, n (%)	764(25.0)	171(28.0)	333(24.3)	260(24.1)	0.152
Laboratory factors					
Glucose (mmol/L)	5.6±1.6	4.7±0.4	5.1±0.6	6.7±2.1	<0.001
HbA1c (%)	6.3±1.1	5.4±0.2	6.0±0.2	7.3±1.2	<0.001
Creatinine (μmol)	73.6±14.1	73.5±14.1	73.3±13.1	74.1±15.2	0.335
hsCRP (μmol/L)	1.5(0.8-2.9)	1.1(0.6-2.2)	1.5(0.8-2.9)	1.7(0.9-3.3)	<0.001
TC (mmol/L)	4.13±1.02	4.00±1.00	4.18±1.00	4.13±1.05	0.001
HDL-C (mmol/L)	1.07±0.28	1.10±0.30	1.09±0.27	1.05±0.27	<0.001
LDL-C (mmol/L)	2.46±0.88	2.37±0.86	2.51±0.87	2.46±0.89	0.003
TG (mmol/L)	1.48(1.09-2.03)	1.38(1.00-1.85)	1.44(1.09-1.98)	1.59(1.17-2.18)	<0.001
LVEF (%)	63.3±7.9	64.0±6.9	63.2±8.4	63.0±7.8	0.026
GS	26(9-44)	24(8-34)	24(8-40)	32(12-56)	<0.001
Prior Medications					
Aspirin, n (%)	2657(86.9)	519(85.1)	1203(87.8)	935(86.8)	0.249
Statins, n (%)	2193(71.7)	423(69.3)	978(71.4)	792(73.5)	0.171
ACEIs/ARBs, n (%)	798(26.1)	149(24.4)	364(26.6)	285(26.5)	0.572
β-blockers, n (%)	1598()	294(48.2)	721(52.6)	573(53.6)	0.112

Data were expressed as mean ± SD, median with 25th and 75th percentile or n (%).

BMI: body mass index; HT: hypertension; CAD: coronary artery disease; HbA1c: haemoglobin A1c; hsCRP: high sensitive C-reactive protein; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; GS:gensini score; ACEIs: angiotensin-converting enzymes; ARBs: angiotensin receptor blocker

Table 2. Cox regression models in predicting cardiovascular events according to different glucose metabolism

Diabetic status (n, events/subjects)	HR (95%CI)		
	Unadjusted model	model 1	model 2
NGR (46/610)	Ref	Ref	Ref
Pre-DM (135/1379)	1.31 (0.94-1.83)	1.29 (0.92-1.81)	1.25 (0.89-1.76)
DM (127/1077)	*1.56 (1.11-2.19)	*1.53 (1.09-2.15)	*1.44 (1.02-2.04)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus;

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease, Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride and high sensitive C-reactive protein;

Table 3. Cox Regression Models in Predicting cardiovascular events according to different status of glucose metabolism and atherogenic dyslipidemia

DM/AD category	Events/Subjects 308/3057	HR (95%CI) Crude Model	HR (95%CI) Adjusted Model
NGR, Non-AD	31/477	Ref	Ref
Pre-DM, Non-AD	92/1005	1.42 (0.94-2.13)	1.35 (0.90-2.04)
DM, Non-AD	84/741	*1.75 (1.16-2.64)	*1.62 (1.06-2.46)
NGR, AD	15/133	1.74 (0.94-3.22)	1.74 (0.94-3.24)
Pre-DM, AD	43//365	*1.81 (1.14-2.88)	*1.73 (1.08-2.76)
DM, AD	43/336	*1.95(1.23-3.09)	*1.81 (1.13-2.91)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; AD: atherogenic dyslipidemia;

Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease. Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, and high sensitive C-reactive protein;

Figure legends

Figure 1 Flowchart of the study. CAD, coronary artery disease; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; NGR: normal glucose regulation; Pre-DM, pre-diabetes mellitus; DM, diabetes mellitus.

Figure 2 Coronary severity in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

* for $p<0.05$; ** for $p<0.01$

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

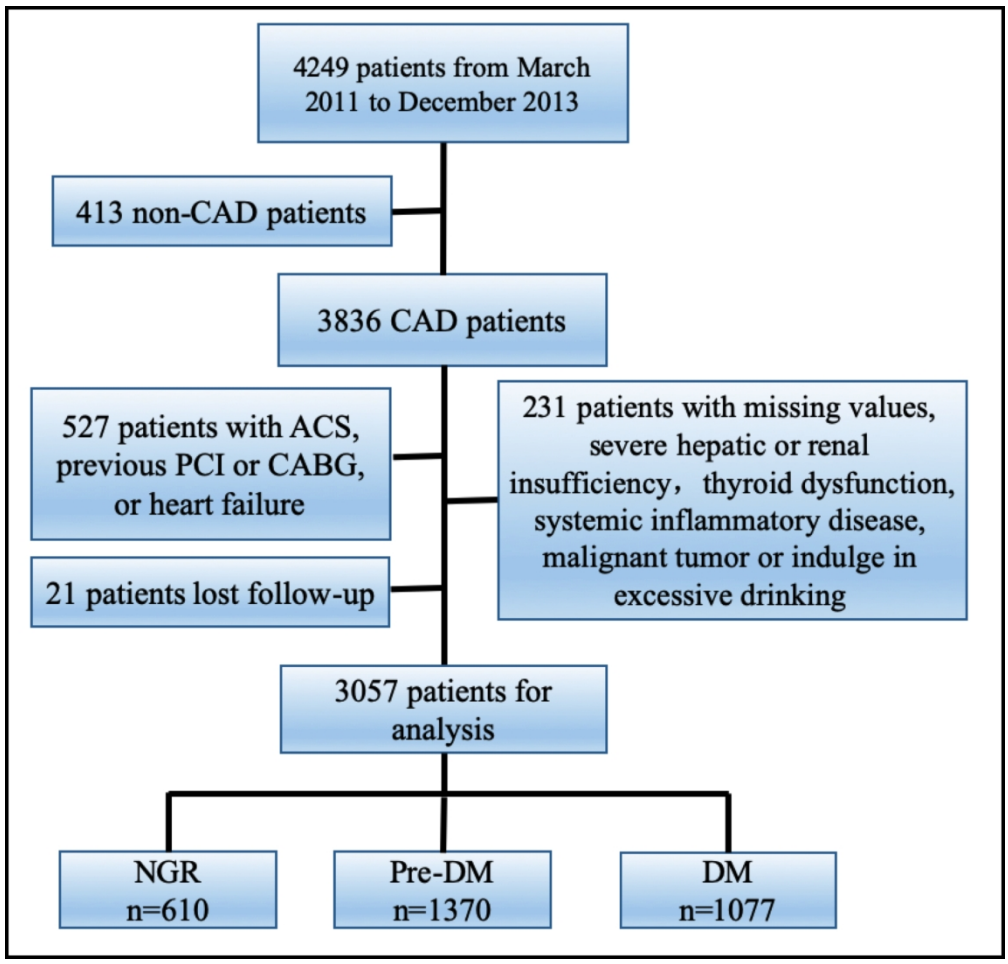

Figure 1 Flowchart of the study.

188x179mm (300 x 300 DPI)

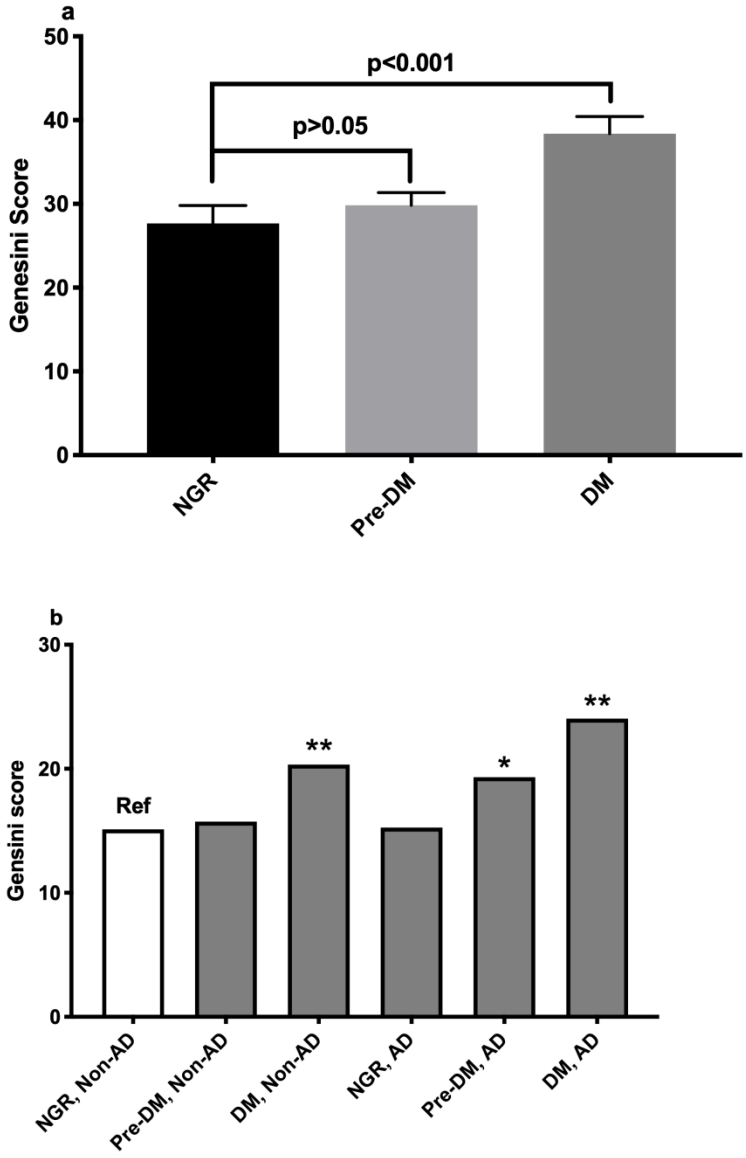

Figure 2 Coronary severity in participants according to a. different glucose metabolism; b. different status of glucose metabolism and atherogenic dyslipidemia * for p<0.05; ** for p<0.01

174x269mm (300 x 300 DPI)

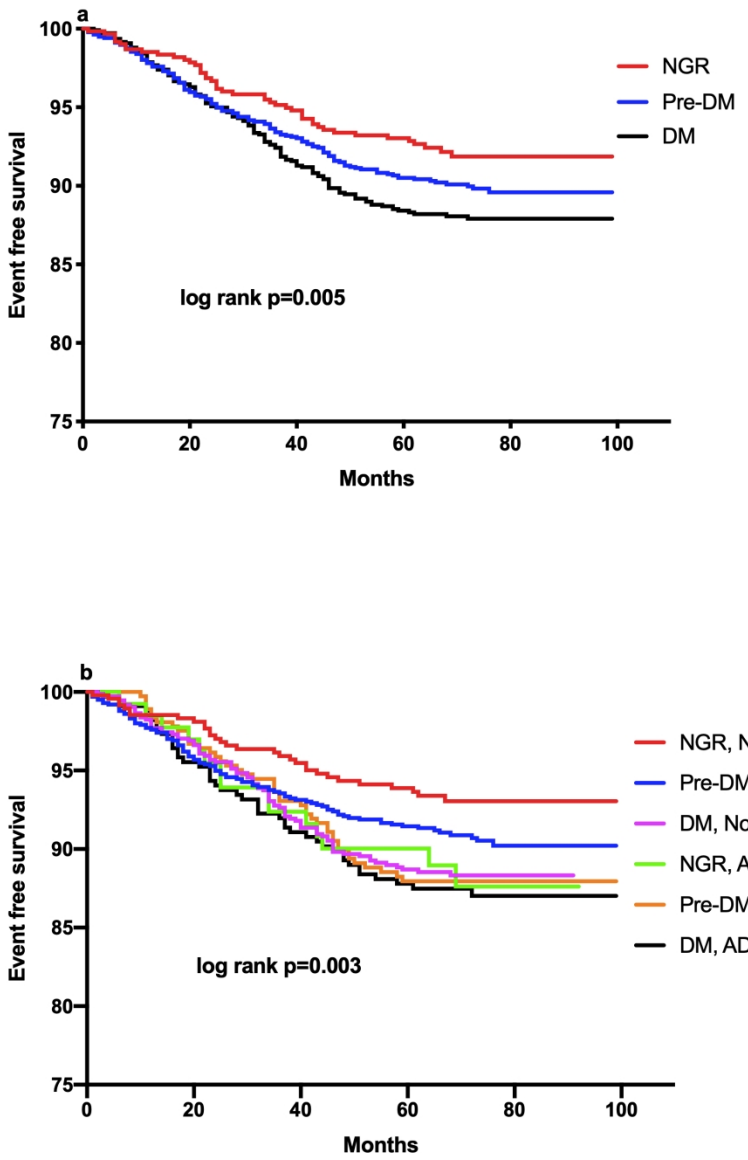

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to a. different glucose metabolism; b. different status of glucose metabolism and atherogenic dyslipidemia

183x250mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	6-7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6-7
		(c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7 6-7 7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Prognostic importance of atherogenic dyslipidemia in patients with stable coronary artery disease and pre-diabetes: a prospective, large Chinese cohort study

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Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Nutrition and metabolism
Keywords:	Lipid disorders < DIABETES & ENDOCRINOLOGY, General diabetes < DIABETES & ENDOCRINOLOGY, Coronary heart disease < CARDIOLOGY

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Title: Prognostic importance of atherogenic dyslipidemia in patients with stable coronary artery disease and pre-diabetes: a prospective, large Chinese cohort study

Running Title: lipid, glucose and outcomes

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Abstract

Objective: The aim of the study is to investigate the impacts of triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) dyslipidemia on prognosis in coronary artery disease patients with different glucose metabolism status.

Design: An observational cohort study

Setting/Participants: A total of 3057 patients with stable coronary artery disease (CAD) were consecutively enrolled and divided into 3 groups according to different glucose metabolism status. Atherogenic dyslipidemia (AD) was defined as TG≥1.7mmol/L and HDL-C<1.0mmol/L for man or <1.3mmol/L for women. These patients were further classified into 6 subgroups by status of atherogenic dyslipidemia. All subjects were followed up for the cardiovascular events (CVEs).

Primary outcome measure: The primary endpoints (CVEs) were cardiovascular mortality, non-fatal myocardial infarction and stroke.

Results: During a median follow-up of 6.1 years, 308 (10.1%) CVEs occurred. No significant difference in occurrence of CVEs was observed between NGR and Pre-DM groups [Hazard Ratio (HR): 1.25, 95% confidence interval (CI): 0.89-1.76] while DM group presented 1.45-fold higher risk of CVEs (HR:1.45, 95%CI: 1.02-2.05). When the participants were categorized according to combined status of two parameters, the cardiovascular risk was significantly elevated in Pre-DM or DM plus AD group compared with the NGR plus Non-AD group (HR: 1.76, 95%CI: 1.10-2.80 and HR: 1.87, 95%CI: 1.17-2.98).

Conclusions: The present study indicated that the presence of atherogenic dyslipidemia have a significant impact on CVEs in Pre-DM.

Keywords: triglyceride, HDL-C, pre-diabetes, prognosis

Strengths and limitations of this study

- Fill the gap of knowledge on the predictive value of atherogenic dyslipidemia in patients with impaired glucose metabolism.
- Using hard endpoints during a relatively long follow-up period.
- Giving evidence on treatment strategies of patients with diabetes and coronary artery disease.
- For inevitable reasons, restricted to the predictive value of baseline parameters.
- Studies in different populations are in need.

Introduction

Dyslipidemia is one of the key drivers in atherogenesis. Lipid lowering therapy targeting at low density lipoprotein cholesterol (LDL-C) has been proved to be efficient in decreasing the progression of arteriosclerotic cardiovascular disease (ASCVD) [1]. Moreover, strong evidence in epidemiological, genetic and prospective cohort studies verifies that high triglyceride (TG) and/or low levels of high density lipoprotein cholesterol (HDL-C) are associated with cardiovascular disease（CVD）risk [2-4]. It has been demonstrated in large-scale clinical trials that hypertriglyceridemia was associated with increased cardiovascular events (CVEs) [5]. However, clinical trials about therapeutic interventions towards low HDL-C provided fewer convincing results. Anacetrapib reduced CVEs by 9% in the Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) study but it was not clear whether the risk reduction was attributed to the increase in HDL-C [6].

Type 2 diabetes mellitus (T2DM) is also one of the main risk factors of CVD and with lipid profiles that are characterized as high TG accompanied by low HDL-C [7]. Previous studies indicated that individuals with atherogenic dyslipidemia (AD) presented higher risk of CVD in DM patients [8]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with a combination of high baseline TG (≥204 mg/dL, highest tertile and a low baseline HDL-C (≤34 mg/dL, lowest tertile) showed possible benefit from fenofibrate plus simvastatin therapy compared to simvastatin alone [9]. Standards of medical care in diabetes from American Diabetes Association (ADA) also recommended intensify lifestyle therapy and optimize glycemic control for patients with elevated TG levels and/or low HDL cholesterol [10].

Pre-diabetes (Pre-DM) is an abnormal glucose regulation status with high predisposition to developing T2DM [11]. Pre-DM subjects had similar lipid profile as DM [12]. However, the prognosis of Pre-DM patients with coronary artery disease (CAD) has less been examined.

Also, whether the Pre-DM alone or accompanied by AD can increase CVD risk in patients with CAD is lacking. The aim of the study is to test the hypothesis that Pre-DM plu sAD had a significant impact on cardiovascular outcomes in patients with angiography-proven CAD.

Materials and Methods

Study Design and Participants

Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Informed written consents were obtained from all patients enrolled in this study.

As described in the flowchart (Fig. 1), from March 2011 to November 2013, 4249 consecutive patients scheduled for coronary angiography because of angina-like chest pain and/or positive treadmill exercise test or clinically suspected CAD was evaluated for the study**.** Among these patients, 413 were excluded because they are not angiography-proven CAD (coronary stenosis ≥50% of at least one coronary artery). Other patients were excluded for following reasons: 527 had acute coronary syndrome (ACS), previous percutaneous coronary coronary artery intervention (PCI) and bypass grafting (CABG) or heart failure; 231 patients were with severe liver and/or renal insufficiency, thyroid dysfunction, systematic inflammatory disease, malignant disease, or indulge in excessive drinking. 21 patients lost follow-up. Patients were followed up at 6 months' intervals by means of interviewing directly or using telephone. Trained nurses or physicians who were blinded to the clinical data fulfilled the interview. The primary endpoints (CVEs) were cardiovascular mortality, non-fatal myocardial infarction (MI) and stroke. Non-fatal myocardial infarction was diagnosed as positive cardiac troponins along with typical chest pain or typical electrocardiogram serial changes. Stroke was diagnosed by the presence of typical symptoms and imaging. Cardiovascular mortality was defined as death

mainly caused by MI, congestive heart failure, stroke, malignant arrhythmia and other structural or functional cardiac diseases.

DM was diagnosed by fasting plasma glucose (FPG) ≥7.0 mmol/L or the 2-h plasma glucose of the oral glucose tolerance test ≥11.1mmol/L or currently using hypoglycaemic drugs or insulin. Pre-DM was diagnosed when participants who had no self-reported DM but met the diagnostic criteria of Pre-DM [13]. Patients who were without DM or Pre-DM were defined as normal glucose regulation (NGR). Atherogenic dyslipidemia (AD) was defined as TG≥1.7mmol/L and HDL-C<1.0mmol/L for man or <1.3mmol/L for women. Hypertension was defined as a self-reported hypertension, currently taking antihypertensive drugs or recorded systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg for three or more consecutive times. Information of other disease, family history, and prior therapy of every patient was collected from self-reported medical history.

Laboratory Analysis

Blood samples were obtained from each patient from the cubital vein after at least 12-h fasting. Concentrations of total cholesterol (TC), TG, LDL-C, HDL-C were measured using automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) in an enzymatic assay. The concentrations of glucose were measured by enzymatic hexokinase method. HbA1c was measured using Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan).

Evaluation of Coronary Severity

Angiographic data were evaluated from catheter laboratory records by 3 experienced interventional cardiologists according to our previous studies [14]. The Gensini score (GS) was calculated as previously described [15].

Statistical Analysis

The values were expressed as the mean±SD or median (Q1–Q3 quartiles) for the continuous variables and the number (percentage) for the categorical variables. The Kolmogorov–Smirnov

test was used to test the distribution pattern. The differences of clinical characteristics between groups were analyzed using the student's t test, analysis of variance, or nonparametric test, chi-squared statistic test or fisher exact test where appropriate. The event-free survival rates among groups were estimated by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratios (HRs). Adjust variables were traditional cardiovascular risk factors including age, sex, body mass index (BMI), smoking, hypertension, family history of CAD, GS, left ventricular ejection fraction (LVEF), LDL-C, HDL-C, TG, high sensitive C-reactive protein and baseline statins. A p-value <0.05 was considered statistically significant. The statistical analyses were performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

As presented in Fig. 1, among 3057 subjects, 20.0%, 44.8%, and 35.2.0% were diagnosed as NGR, Pre-DM, and DM respectively according to ADA criteria. The baseline characteristics of the study participants were shown in Table 1. The age, BMI, glucose, HbA1c, TG, and high-sensitivity C-reactive protein (hsCRP) were positively associated with the status of glucose metabolism from NGR to DM (all P<0.001). The proportion of patients with hypertension was elevated from NGR to DM (p<0.001). Patients with Pre-DM and DM had higher levels of TC and LDL-C than the NGR group. Meanwhile, DM but not Pre-DM patients had significantly lower levels of HDL-C and LVEF than NGR population. There was no significant difference regarding sex, smoking, drinking, family history of CAD, creatinine, and medication prescriptions among the three groups (p>0.05).

The coronary severity was compared among different status of glucose metabolism. As shown in Fig. 2a and 2b, DM group had significantly higher GS ($p<0.05$) while there was no significant difference between Pre-DM and NGR groups ($P>0.05$). We further divided the patients into the six groups according to status of glucose metabolism and AD (NGR plus Non-AD; Pre-DM plus Non-AD; DM plus Non-AD; NGR plus AD; Pre-DM plus AD; DM plus AD). We set NGR and Non-AD group as reference and compared its GS with that of other groups. All the other groups had higher GS than the reference group (all $p<0.05$) except Pre-DM plus Non-AD and NGR plus AD group ($p>0.05$ respectively). As shown in Supplemental Table S1, multivariate regression logistic regression analysis revealed that DM group was independently associated with high GS (median as cut-off, $p<0.05$). Pre-DM plus AD group and DM plus AD group were also independently associated with presence of high GS(all $p<0.05$, Supplemental Table S2).

Over a median follow-up time of 6.1 years (5.1 to 7.5 years), 308 CVEs occurred (112 died, 73 suffered nonfatal MI, 123 had nonfatal strokes). The prevalence of CVEs in NGR, Pre-DM, and DM group was 7.5%, 9.9%, and 11.8%, respectively. Kaplan–Meier analysis (Fig. 3a) showed that DM subjects had the lowest event-free survival rate among the 3 groups ($p<0.05$) while there was no significant difference between that of Pre-DM and NGR groups ($p>0.05$)**.** However, when the patients were evaluated according to both glucose metabolism and AD status: DM plus Non-AD, Pre-DM plus AD, and DM plus AD groups had significantly lower cumulative event-free survival rates compared with the reference group (NGR plus Non-AD group, Fig. 3b, all $p<0.05$ respectively). As presented in Table 2, univariate Cox regression models showed that patients with DM had 1.45-fold higher risk of CVEs than NGR subjects [HR:1.45, 95% coincidence interval (CI):1.02-2.05, $p<0.05$]. The Gensini score was also associated with CVEs [HR:1.004, 95% CI:1.001-1.008, $p<0.05$]. Additional adjustment for confounding variables including Gensini score did not change the significance of association.

The presence of Pre-DM did not show increase in CVEs risk when compared with NGR group ($p>0.05$). Moreover, multivariate Cox regression analyses according to both glucose metabolism and AD status indicated that patients in DM plus non-AD, Pre-DM plus AD, and DM plus AD groups had1.68-fold (95%CI:1.11-2.56), 1.76-fold (95%CI: 1.10-2.80), and 1.87-fold (95%CI: 1.17-2.98) higher risk of CVEs (Table 3, all $p<0.05$ respectively).

Discussion

The causality of high TG and/or low HDL-C to ASCVD has been controversial during the past decades. Previous prospective studies have shown that patients with high TG combined with low HDL-C may be more likely to develop ASCVD, especially in those with DM [16]. In this study, we investigated the impact of AD on cardiovascular outcomes in stable, angiography-proven CAD patients in different glucose metabolism status. We found that patients with DM but not those with Pre-DM had more severe coronary stenosis and higher risk of CVEs when the patients were simply divided into the three groups: DM, Pre-DM, and NGR. Interestingly, when patients were categorized according to both status of glucose metabolism and AD, patient with Pre-DM plus AD had higher GS and 1.76-fold increased risk of CVEs compared with that in subjects with NGR and Non-AD. Thus, our study, for the first time, suggested that the presence of Pre-DM had significant impact on cardiovascular outcomes when combined with AD.

High TG and low HDL-C are common lipid abnormalities among adult population, especially in Chinese subjects. According to DYSlipidemia International Study (DYSIS), 41.8% patients had high TG and 31.9% patients had low HDL-C among the Chinese population in primary prevention [17]. Additionally, studies about lowering TG and raising HDL-C on reducing CVD risk were with inconsistent results [6,9]. For example, fibrates did not associate with conclusive effect in ASCVD reduction in ACCORD trials while patients who received 2

g of icosapent ethyl twice daily had lower risk of ischemic events in Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [9,18]. However, in randomized controlled trials (RCTs), cholestery l ester transfer protein (CETP) inhibitors, which aimed at increasing plasma HDL-C, failed to reduce CVEs rates [9, 19-21]. In the meanwhile, Mendelian analysis involving about 20,000 MI individuals and 50,000 controls demonstrated that 1 SD increase in TG levels was associated with 54% increase risk of MI [22]. In contrast, no such association was found for patients with low baseline levels of HDL-C [3]. Moreover, high TG and low HDL-C were often regarded as a whole and defined as AD or metabolic dyslipidemia in many studies. In the EPIC-Norfolk prospective population study, healthy men with AD had 61% higher risk of CAD than those with normal TG and HDL [23]. Of noted, patients with obesity, insulin resistance or other metabolic abnormalities had higher prevalence of high TG and/or low HDL-C [24].

DM was the most common metabolic disease in the 21st century and approximately 415 million adults were with T2DM worldwide [25]. Prevalence of total diagnosed and undiagnosed diabetes in China also reached 10.9% in 2013 [26]. What's more, CAD was a common comorbidity and increased mortality in patients with DM. According to previous studies, DM patients without angiography-proven CAD showed low risk of MI or CVEs (defined as death, cardiac death, and MI), but the DM and CAD combination further increased the risk of ischemic stroke [27-28]. In our previous studies, among patients with established CAD, individuals with DM were associated with significantly higher risk of worse prognosis when they were combined with other CAD risk factors, including hypertension and Lp(a)-hyperlipoproteinemia [14, 29]. Therefore, in the present study, among patients with stable CAD, identifying whether AD is a risk factor for worse prognosis might be crucial.

In strong heart study, high TG plus low HDL levels were associated with a 1.54-fold greater occurrence risk for CAD and a 2.13-fold occurrence risk for stroke in community based

African Americans with DM [8]. In a large cohort of 28,318 DM subjects, increased CAD risk was observed in both men and women with AD [16]. In the ACCORD trial, for participants with DM, fenofibrate plus simvastatin 40mg exhibited a 31% reduction in CVEs in the subgroup with baseline high TG and low HDL-C [9].

In fact, more attention has recently been paid to the prevention of DM and the clinical characters in the early phase of impaired glucose metabolism. Pre-DM was an intermediate state between NGR and DM and with high predisposition to develop DM. This metabolic condition was often reversible. The rate of individuals with Pre-DM was almost three times higher than DM worldwide and in China (35.7% vs.10.9% in China) [25,30]. The prevalence of Pre-DM and CVEs risk have long been debating. Despite the differences of cut-off point in diagnose of pre-DM, studies and meta-analysis using blood glucose and HbA1c according to 2003 ADA guideline also had different results [31-32]. In our study population, as previously reported, the predictive value of Pre-DM for CVEs was less significant, which was also consistent with studies conducted by Liu et al and Qiu et al [14, 33]. In the present study, 21.8%, 26.6% and 31.2% of patients had AD in NGR, Pre-DM and DM groups. Both Pre-DM and DM groups had higher rate of AD than NGR group. As the main findings of our study, stable CAD patients with Pre-DM plus AD had higher GS and increased risk of CVEs while no statistically significant difference were observed between Pre-DM alone and NGR plus Non-AD groups. Therefore, similar attention should be given to patients with Pre-DM and DM when they were with AD.

The present study had several virtues compared with previous published reports. Very few studies have evaluated the differences of coronary severity and outcomes according to both status of glucose metabolism and AD, especially in those with stable CAD. In addition, previous studies were also limited by the fact that the risk of high TG and/ or low HDL-C levels were analyzed separately within DM or NGR population, neglecting of the potential high risk

which was caused by the interaction of lipid and glucose. Moreover, there were no such studies about the impacts of AD on cardiovascular outcomes in CAD patients with Pre-DM. Apparently, a large sample size of angiography-proven CAD patients with high prevalence of DM and pre-DM were enrolled in the present study. Hard endpoints containing nonfatal strokes, nonfatal MI, and cardiovascular mortality were also observed during a relatively long follow-up period. Thereby, our study provided important information regarding dyslipidemia, pre-DM and outcome, which may influence our treatment decision for CAD patients with pre-DM.

Nevertheless, there are still several limitations in the present study. Firstly, this is a single center study among Chinses patients with stable CAD. Secondly, we measured TG, HDL-C and glucose metabolism status only at the baseline. The follow-up levels of TG/HDL-C may also be clinically significant. According to previous study, during the follow-up period, a small proportion of subjects with Pre-DM may develop DM each year [34]. The increased CAD severity and CVEs may be overestimated in the Pre-DM group. Thirdly, we did not assess the all metabolic factors and parameters about insulin resistance due to the features of patients in our study. Fourthly， although AD plus Pre-DM group did not present increased CVEs risk, there is possibility that the result missed the statistical significance level due to smaller number of subjects. Hence, further studies with larger sample size may be needed.

In conclusion, in our large sample size with long-term follow-up study, data indicated that the Pre-DM patients with AD had significantly higher risk of CVEs, suggesting that treatment and lifestyle management towards AD in Pre-DM patients may also be crucial for improving clinical outcomes.

Contributors

Study concept and design: Professor Jian-Jun-Li, Dr Ying Gao and Dr Jing-Lu Jin. Acquisition of data: Prof. Jian-Jun-Li, Dr Ye-Xuan Cao and Dr Jing-Lu Jin. Analysis and interpretation of

data: Dr Ying Gao and Dr Jing-Lu Jin. Drafting of the manuscript: Dr Jing-Lu Jin. Critical revision of the manuscript for important intellectual content: Professor Jian-Jun-Li. Statistical analysis: Dr Jing-Lu Jin. Obtained funding: Professor Jian-Jun-Li and Dr Ying Gao. Administrative, technical or material support: Drs Li-Guo Wu, Xiang-Dong You, Yuan-Lin Guo, Na-Qiong Wu, Cheng-Gang Zhu, Hui-Hui Liu, Rui-Xia Xu and Miss Jing Sun and Qian Dong. Study supervision: Prof Jian-Jun Li.

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Competing interests

None declared

Patient consent

Obtained.

Ethics approval

The study was performed according to the Declaration of Helsinki, and the hospital ethics review board (Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China) approved the protocol.

Data sharing statement

The technical appendix, statistical code and data set are available from the corresponding author.

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Figure Legends

Figure 1 Flowchart of the study

Figure 2 Coronary severity in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia * for $p<0.05$

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

Tables

Table 1. Baseline characteristics of the participants according to different glucose metabolism

	Total n=3057	NGR n=610	Pre-DM n=1370	DM n=1077	P
Clinical factors					
Age, years	58.5±9.8	55.5±10.0	58.8±9.4	59.9±9.8	<0.001
Male, n (%)	2149(70.3)	438(71.8)	956(69.8)	755(70.1)	0.651
BMI (kg/m^2)	25.6±3.2	25.0±3.0	25.5±3.2	26.1±3.2	<0.001
HT, n (%)	1904(62.3)	339(55.6)	804(58.7)	761(70.7)	<0.001
Family history of CAD	494(16.2)	112(18.4)	221(16.1)	161(14.9)	0.188
Current Smoker, n (%)	1580(51.7)	307(50.3)	714(52.1)	559(51.7)	0.751
Drinking, n (%)	764(25.0)	171(28.0)	333(24.3)	260(24.1)	0.152
Revascularization, n (%)	2182(71.4)	432(70.8)	992(72.4)	758(70.4)	0.514
Laboratory factors					
Glucose (mmol/L)	5.6±1.6	4.7±0.4	5.1±0.6	6.7±2.1	<0.001
HbA1c (%)	6.3±1.1	5.4±0.2	6.0±0.2	7.3±1.2	<0.001
Creatinine (μmol)	73.6±14.1	73.5±14.1	73.3±13.1	74.1±15.2	0.335
hsCRP (μmol/L)	1.5(0.8-2.9)	1.1(0.6-2.2)	1.5(0.8-2.9)	1.7(0.9-3.3)	<0.001
TC (mmol/L)	4.13±1.02	4.00±1.00	4.18±1.00	4.13±1.05	0.001
HDL-C (mmol/L)	1.07±0.28	1.10±0.30	1.09±0.27	1.05±0.27	<0.001
LDL-C (mmol/L)	2.46±0.88	2.37±0.86	2.51±0.87	2.46±0.89	0.003
TG (mmol/L)	1.48(1.09-2.03)	1.38(1.00-1.85)	1.44(1.09-1.98)	1.59(1.17-2.18)	<0.001
LVEF (%)	63.3±7.9	64.0±6.9	63.2±8.4	63.0±7.8	0.026
GS	26(9-44)	24(8-34)	24(8-40)	32(12-56)	<0.001
Prior Medications					
Aspirin, n (%)	2657(86.9)	519(85.1)	1203(87.8)	935(86.8)	0.249
Statins, n (%)	2193(71.7)	423(69.3)	978(71.4)	792(73.5)	0.171
ACEIs/ARBs, n (%)	798(26.1)	149(24.4)	364(26.6)	285(26.5)	0.572
β-blockers, n (%)	1598(52.3)	294(48.2)	721(52.6)	573(53.6)	0.112
Antidiabetic drug					
OADs, n(%)	648(21.2)	-	-	648(60.2)	
Insulin, n(%)	382(12.5)	-	-	382(35.5)	

Data were expressed as mean ± SD, median with 25th and 75th percentile or n (%).

BMI: body mass index; HT: hypertension; CAD: coronary artery disease; HbA1c: haemoglobin A1c; hsCRP: high sensitive C-reactive protein; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; LVEF: left ventricular ejection fraction;

GS:gensini score; ACEIs: angiotensin-converting enzymes; ARBs: angiotensin receptor blocker; OADs: oral antidiabetic drug.

Table 2. Cox regression models in predicting cardiovascular events according to different glucose metabolism

Diabetic status (n, events/subjects)	HR (95%CI)		
	Unadjusted model	model 1	model 2
NGR (46/610)	Ref	Ref	Ref
Pre-DM (135/1379)	1.31 (0.94-1.83)	1.29 (0.92-1.81)	1.25 (0.89-1.76)
DM (127/1077)	*1.56 (1.11-2.19)	*1.53 (1.09-2.15)	*1.45 (1.02-2.05)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus;

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease, Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride, high sensitive C-reactive protein, and baseline statins;

Table 3. Cox Regression Models in Predicting cardiovascular events according to different status of glucose metabolism and atherogenic dyslipidemia

DM/AD category	Events/Subjects 308/3057	HR (95%CI) Crude Model	HR (95%CI) Adjusted Model
NGR, Non-AD	31/477	Ref	Ref
Pre-DM, Non-AD	92/1005	1.42 (0.94-2.13)	1.40 (0.92-2.10)
DM, Non-AD	84/741	*1.75 (1.16-2.64)	*1.68 (1.11-2.56)
NGR, AD	15/133	1.74 (0.94-3.22)	1.74 (0.94-3.23)
Pre-DM, AD	43//365	*1.81 (1.14-2.88)	*1.76 (1.10-2.80)
DM, AD	43/336	*1.95(1.23-3.09)	*1.87 (1.17-2.98)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; AD: atherogenic dyslipidemia;

Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease, Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, high sensitive C-reactive protein, and baseline statins;

Figure legends

Figure 1 Flowchart of the study. CAD, coronary artery disease; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; NGR: normal glucose regulation; Pre-DM, pre-diabetes mellitus; DM, diabetes mellitus.

Figure 2 Coronary severity in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

* for $p<0.05$; ** for $p<0.01$

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

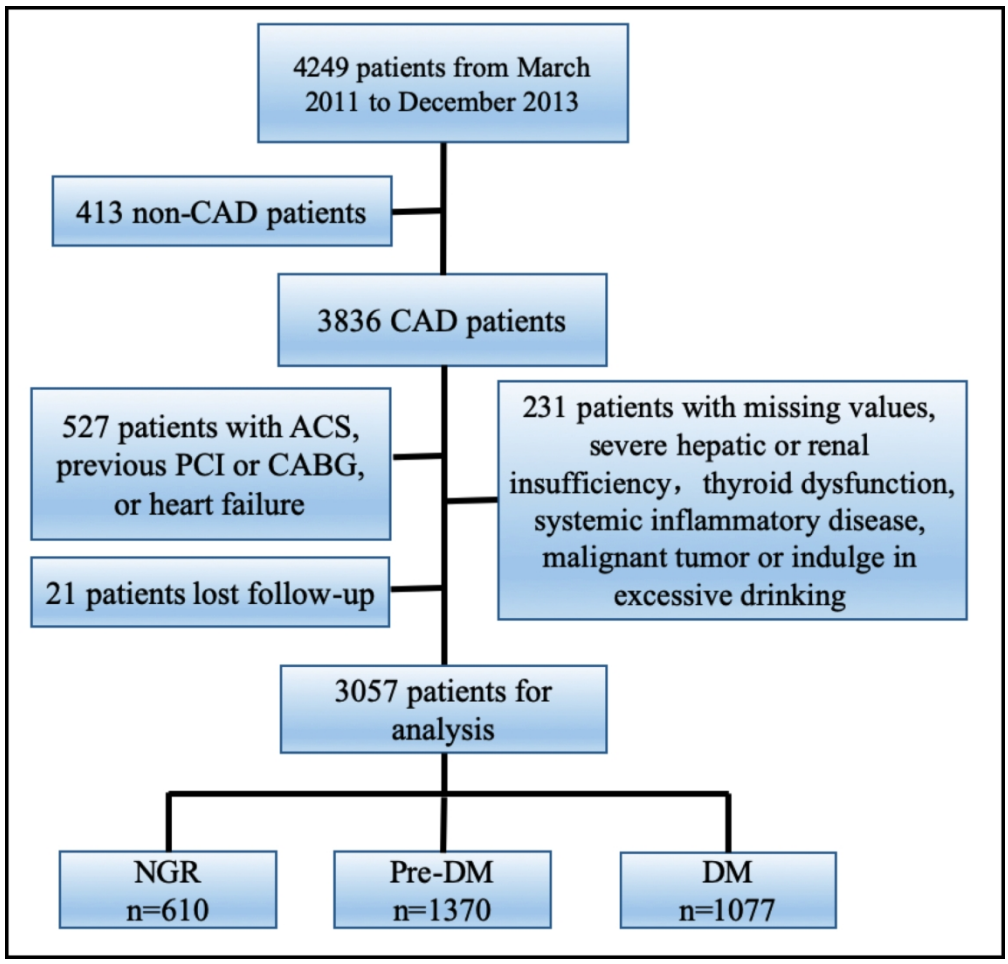

Figure 1 Flowchart of the study.

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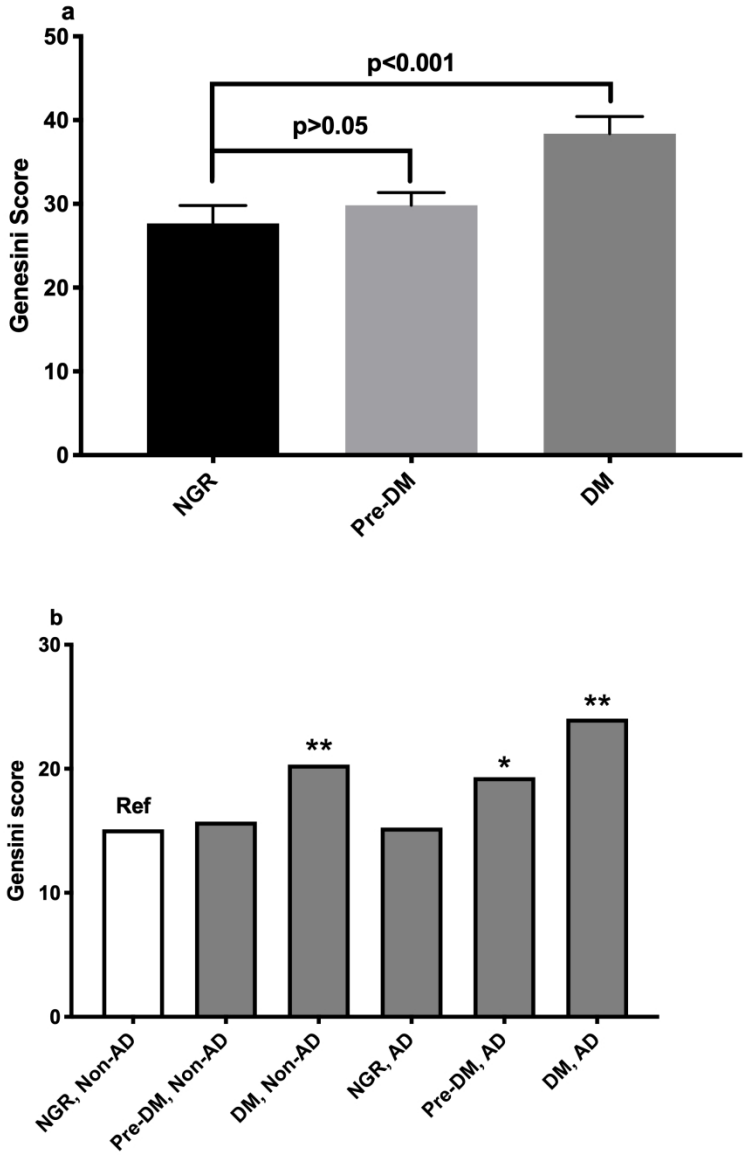

Figure 2 Coronary severity in participants according to a. different glucose metabolism; b. different status of glucose metabolism and atherogenic dyslipidemia * for p<0.05; ** for p<0.01

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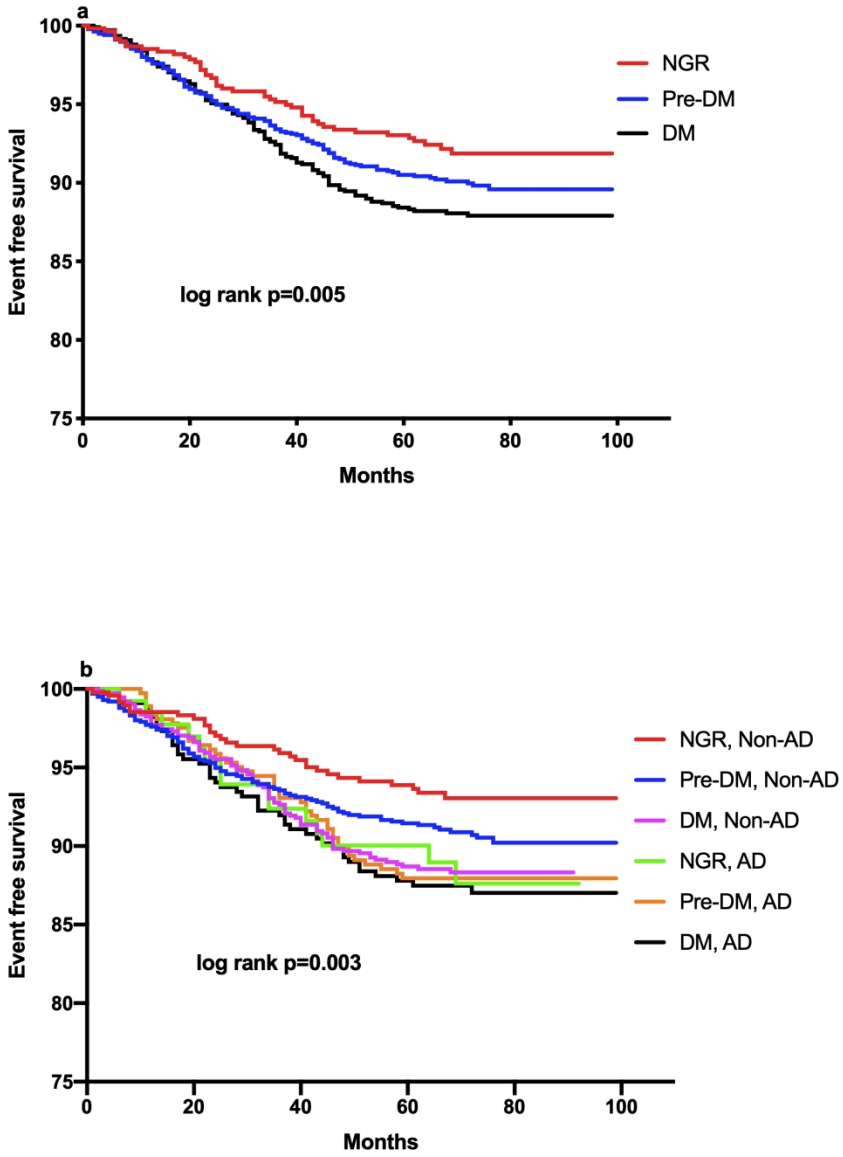

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to a. different glucose metabolism; b. different status of glucose metabolism and atherogenic dyslipidemia

183x250mm (300 x 300 DPI)

Supplemental Data.

Supplemental Table S1 Logistic regression analysis regarding the association between glucose metabolism status and high Gensini score (median as cut-off)

	OR (95%CI)	
DM category	**Crude Model**	**Adjusted Model**
NGR	Ref	Ref
Pre-DM	1.03 (0.85-1.24)	0.97(0.80-1.18)
DM	*1.55 (1.27-1.90)	*1.42 (1.16-1.75)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease. Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, triglyceride, high density lipoprotein cholesterol, high sensitive C-reactive protein and baseline statins;

Supplemental Table S2 Logistic regression analysis regarding the association between combined status of glucose metabolism status and stherogenic dyslipidemia and high Gensini Score (median as cut-off)

	OR (95%CI)	
DM/AD category	**Crude Model**	**Adjusted Model**
NGR, Non-AD	Ref	Ref
Pre-DM, Non-AD	0.92 (0.74-1.15)	0.89 (0.71-1.11)
DM, Non-AD	*1.51(1.20-1.90)	*1.43(1.13-1.81)
NGR, AD	1.01(0.69-1.48)	1.01(0.68-1.49)
Pre-DM, AD	*1.39(1.06-1.83)	*1.37(1.04-1.81)
DM, AD	*1.67(1.26-2.21)	*1.64 (1.23-2.19)

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; AD: atherogenic dyslipidemia;

Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease. Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, and high sensitive C-reactive protein, and baseline statins;

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	6-7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6-7
		(c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7 6-7 7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Atherogenic dyslipidemia and cardiovascular events in patients with diabetes or prediabetes and stable coronary artery disease: a prospective, cohort study

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Title: Atherogenic dyslipidemia and cardiovascular events in patients with diabetes or prediabetes and stable coronary artery disease: a prospective, cohort study

Running Title: AD and outcomes in CAD patients with DM or pre-DM

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Abstract

Objective: The aim of the study was to investigate the impacts of triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) dyslipidemia on prognosis in coronary artery disease (CAD) patients with different glucose metabolism status.

Design: An observational cohort study

Setting/Participants: A total of 3057 patients with stable CAD were consecutively enrolled and divided into 3 groups according to different glucose metabolism status. Atherogenic dyslipidemia (AD) was defined as TG≥1.7mmol/L and HDL-C<1.0mmol/L for man or <1.3mmol/L for women. The patients were further classified into 6 subgroups by status of AD. All subjects were followed up for the cardiovascular events (CVEs).

Primary outcome measures: The primary endpoints were cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke.

Results: During a median follow-up of 6.1 years, 308 (10.1%) CVEs occurred. No significant difference in the occurrence of CVEs was observed between NGR and Pre-DM groups [Hazard Ratio (HR): 1.25, 95% confidence interval (CI): 0.89-1.76] while DM group presented 1.45-fold higher risk of CVEs (HR:1.45, 95%CI: 1.02-2.05). When the participants were categorized according to combined status of two parameters, the cardiovascular risk was significantly elevated in Pre-DM or DM plus AD group compared with the NGR plus Non-AD group (HR: 1.76, 95%CI: 1.10-2.80 and HR: 1.87, 95%CI: 1.17-2.98).

Conclusions: The present study suggested that the presence of AD might affect the prognosis in patients with DM or pre-DM and stable CAD.

Keywords: triglyceride, HDL-C, pre-diabetes, prognosis

Strengths and limitations of this study

- This study fills the gap of the current knowledge on the predictive value of atherogenic dyslipidemia in patients with coronary artery diseases and impaired glucose metabolism.
- The study focuses on hard endpoints during a relatively long follow-up period, which might provide reliable information concerning the impact of dyslipidemia on outcomes in such patients.
- This is a single center, observational study among Chinses patients with stable CAD.
- For inevitable reasons, this study is restricted to the predictive value of baseline parameters.
- More studies may be necessary in different kinds of population such as unstable CAD patients and subjects in randomized clinical trials.

Introduction

Dyslipidemia is one of the key drivers in atherogenesis. Lipid lowering therapy targeting at low density lipoprotein cholesterol (LDL-C) has been proved to be efficient in secondary prevention of arteriosclerotic cardiovascular disease (ASCVD) [1]. Moreover, strong evidence from epidemiological, genetic and prospective cohort studies verifies that high triglyceride (TG) and/or low levels of high density lipoprotein cholesterol (HDL-C) are associated with cardiovascular disease(CVD)risk [2-4]. It has been demonstrated in large-scale clinical trials that hypertriglyceridemia was associated with increased cardiovascular events (CVEs) [5]. However, clinical trials about therapeutic interventions in patients afflicted with low HDL-C did not show convincing results. Anacetrapib reduced CVEs by 9% in the Randomized Evaluation of the Effects of Anacetrapib through Lipid-modification (REVEAL) study but it was not clear whether the risk reduction was attributed to the increase in HDL-C [6]. Type 2 diabetes mellitus (T2DM) is also one of the major risk factors of CVD[7]. Atherogenic dyslipidemia (AD), defined as low HDL-C accompanied with elevated TG, is one of the most important comorbidities in T2DM. Previous studies indicated that individuals with AD presented higher risk of CVD in DM patients [8]. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with a combination of high baseline TG (≥204 mg/dL, highest tertile) and low baseline HDL-C (≤34 mg/dL, lowest tertile) showed possible benefit from fenofibrate plus simvastatin therapy compared to simvastatin alone [9]. Standards of medical care in diabetes from American Diabetes Association (ADA) also recommended intensify lifestyle therapy and optimize glycemic control for patients with elevated TG levels and/or low HDL cholesterol [10].

Pre-diabetes (Pre-DM) is an abnormal glucose regulation status with high predisposition to developing T2DM. Pre-DM subjects had similar lipid profile as DM patients. However, the prognosis of Pre-DM patients with coronary artery disease (CAD) was rarely estimated. Also,

evidence about whether the Pre-DM alone or accompanied by AD can increase CVD risk in patients with CAD is lacking. The aim of the study is to test the hypothesis that Pre-DM and DM plus AD had significant impacts on cardiovascular outcomes in patients with angiography-proven CAD.

Materials and Methods

Study Design and Participants

Our study complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital & National Center for Cardiovascular Diseases, Beijing, China). Informed written consents were obtained from all patients who were enrolled in this study.

From March 2011 to November 2013, 4249 consecutive patients were scheduled for coronary angiography because of clinically suspected CAD**.** Among these patients, 413 were excluded because they did not meet the diagnostic criteria of CAD (with a stenosis more than 50% of the at least one major coronary artery). Other exclusion criteria were described in the flowchart (Fig. 1). As reported in detail previously [11.12], patients were followed up for primary endpoints which included cardiovascular mortality, non-fatal myocardial infarction (MI) and stroke.

DM and Pre-DM were diagnosed according to according to ADA criteria [13]. Patients who were without DM or Pre-DM were defined as normal glucose regulation [NGR，fasting plasma glucose <5.6 and hemoglobin A1c (HbA1c) level <5.7%). AD was defined as TG≥1.7mmol/L and HDL-C<1.0mmol/L for man or <1.3mmol/L for women. Hypertension was defined as a self-reported hypertension, currently taking antihypertensive drugs or recorded systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg for three or more consecutive times. Information of other disease, family history, and prior therapy of every patient was also documented.

Laboratory Analysis

Blood samples were obtained from each patient from the cubital vein after at least 12-h fasting. Concentrations of total cholesterol (TC), TG, LDL-C, HDL-C were measured using automatic biochemistry analyzer (Hitachi 7150, Tokyo, Japan) in an enzymatic assay. The concentrations of glucose were measured by enzymatic hexokinase method. HbA1c was measured using Tosoh Automated Glycohemoglobin Analyser (HLC-723G8, Tokyo, Japan).

Evaluation of Coronary Severity

Angiographic data were evaluated from catheter laboratory records by 3 experienced interventional cardiologists according to our previous studies [14]. The Gensini score (GS) was calculated as previously described [15].

Statistical Analysis

The values were expressed as the mean±SD or median (Q1–Q3 quartiles) for the continuous variables and the number (percentage) for the categorical variables. The Kolmogorov–Smirnov test was used to test the distribution pattern. The differences of clinical characteristics between groups were analyzed using the student's t test, analysis of variance, or nonparametric test, chi-squared statistic test or fisher exact test where appropriate. The event-free survival rates among groups were estimated by the Kaplan–Meier method and compared by the log-rank test. Univariate and multivariate Cox regression analyses were performed to calculate the hazard ratios (HRs). Adjust variables were traditional cardiovascular risk factors including age, sex, body mass index (BMI), smoking, hypertension, family history of CAD, GS, left ventricular ejection fraction (LVEF), LDL-C, HDL-C, TG, high sensitive C-reactive protein and baseline statins. A p-value <0.05 was considered statistically significant. The statistical analyses were performed with SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA).

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Results

As presented in Fig. 1, 20.0%, 44.8%, and 35.2% of 3057 subjects were diagnosed as NGR, Pre-DM, and DM respectively according to ADA criteria. The baseline characteristics of the study participants were shown in Table 1. The age, BMI, glucose, HbA1c, TG, and high-sensitivity C-reactive protein (hsCRP) and proportion of hypertension were elevated from NGR to DM (all P<0.001). Patients with Pre-DM and DM had elevated levels of TC and LDL-C than the NGR group. Meanwhile, NGR patients had significantly higher levels of HDL-C and LVEF than DM population. There was no significant difference regarding other demographic and laboratory parameters among the three groups (p>0.05).

The coronary severity was compared among different status of glucose metabolism. As shown in Fig. 2a and 2b, DM group had significantly higher GS (p<0.05) while there was no significant difference between Pre-DM and NGR groups (P>0.05). We further divided the patients into the six groups according to status of glucose metabolism and AD (NGR plus Non-AD; Pre-DM plus Non-AD; DM plus Non-AD; NGR plus AD; Pre-DM plus AD; DM plus AD). We set NGR and Non-AD group as reference and compared its GS with that of other groups. All the other groups had higher GS than the reference group (all p<0.05) except Pre-DM plus Non-AD and NGR plus AD group (p>0.05 respectively). As shown in Supplemental Table S1, multivariate regression logistic regression analysis revealed that DM group was independently associated with high GS (median as cut-off, p<0.05). Pre-DM plus AD group and DM plus AD group were also independently associated with the presence of high GS(all p<0.05, Supplemental Table S2).

Over a median follow-up time of 6.1 years (5.1 to 7.5 years), 308 CVEs occurred, including 112 cardiovascular deaths, 73 nonfatal MI and 123 had nonfatal strokes. 7.5%, 9.9%, and 11.8% of patients had CVEs in NGR, Pre-DM, and DM groups respectively. As indicated in Kaplan–Meier analysis (Fig. 3a), DM subjects had the highest event rate among the 3 groups ($p<0.05$) while there was no significant difference between that of Pre-DM and NGR groups ($p>0.05$). However, when the patients were evaluated according to both glucose metabolism and AD status: DM plus Non-AD, Pre-DM plus AD, and DM plus AD groups had significantly lower cumulative event-free survival rates compared with the reference group (NGR plus Non-AD group, Fig. 3b, all $p<0.05$ respectively). As presented in Table 2, univariate Cox regression models showed that patients with DM had 1.45-fold higher risk of CVEs than NGR subjects [HR:1.45, 95% coincidence interval (CI):1.02-2.05, $p<0.05$]. The Gensini score was also associated with CVEs [HR:1.004, 95% CI:1.001-1.008, $p<0.05$]. Additional adjustment for confounding variables including Gensini score did not change the significance of association. The presence of Pre-DM did not show increase in CVEs risk when compared with NGR group ($p>0.05$). Moreover, multivariate Cox regression analyses according to both glucose metabolism and AD status indicated that patients in DM plus non-AD, Pre-DM plus AD, and DM plus AD groups had1.68-fold (95%CI:1.11-2.56), 1.76-fold (95%CI: 1.10-2.80), and 1.87-fold (95%CI: 1.17-2.98) higher risk of CVEs (Table 3, all $p<0.05$ respectively).

Discussion

The relation of high TG and/or low HDL-C to ASCVD risk has been controversial during the past decades. Previous prospective studies have shown that patients with high TG combined with low HDL-C may be more likely to develop ASCVD, especially in those with DM [16]. In this study, we investigated the impact of AD on cardiovascular outcomes in stable, angiography-proven CAD patients with different glucose metabolism status. We found that

patients with DM but not those with Pre-DM had more severe coronary stenosis and higher risk of CVEs when the patients were simply divided into the three groups: DM, Pre-DM, and NGR. Interestingly, when patients were categorized according to both status of glucose metabolism and AD, individuals with Pre-DM plus AD had higher GS and 1.76-fold increased risk of CVEs than NGR and Non-AD subjects. Thus, our study suggested that the presence of AD may have an impact on cardiovascular outcomes in patients with CAD and DM or Pre-DM.

High TG and low HDL-C are common lipid abnormalities among adult population, especially in Chinese subjects. According to DYSlipidemia International Study (DYSIS), 41.8% patients had high TG and 31.9% patients had low HDL-C among Chinese population [17]. Additionally, studies about reducing CVD risk by lowering TG and raising HDL-C had inconsistent results [6,9]. For example, fibrates did not have conclusive effect in ASCVD risk reduction in ACCORD trials while patients who received 2 g of icosapent ethyl twice daily had lower risk of ischemic events in Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) [9,18]. However, in randomized controlled trials (RCTs), cholestery l ester transfer protein (CETP) inhibitors, which could increase plasma HDL-C, failed to reduce CVEs rates [9, 19-21]. In the meanwhile, Mendelian analysis involving about 20,000 MI individuals and 50,000 controls demonstrated that 1 SD increase in TG levels was associated with 54% increased risk of MI [22]. In contrast, no such association was found for patients with low baseline levels of HDL-C [3]. Moreover, in the EPIC-Norfolk prospective population study, healthy men with AD had 61% higher risk of CAD than those with normal TG and HDL-C [23]. Of noted, patients who were with obesity, insulin resistance or other metabolic abnormalities had higher prevalence of high TG and/or low HDL-C [24].

DM was the most common metabolic disease in the 21st century. Approximately 415 million adults were with T2DM worldwide [25]. Prevalence of total diagnosed and

undiagnosed diabetes in China reached 10.9% in 2013 [26]. What's more, CAD was a common comorbidity in patients with DM. According to previous studies, DM patients without angiography-proven CAD showed low risk of MI or CVEs (defined as death, cardiac death, and MI), but the DM and CAD combination further increased the risk of ischemic stroke [27-28]. In our previous studies, among patients with established CAD, individuals with DM were associated with significantly higher risk of worse prognosis when they were combined with other CAD risk factors, including hypertension and Lp(a)-hyperlipoproteinemia [14, 29]. Therefore, in the present study, among patients with stable CAD under different glucose metabolism status, identifying whether AD is a risk factor for worse prognosis might be crucial. In strong heart study, high TG plus low HDL was associated with a 1.54-fold greater occurrence risk for CAD and a 2.13-fold occurrence risk for stroke in community based African Americans with DM [8]. In a large cohort of 28,318 DM subjects, increased CAD risk was observed in both men and women with AD [16]. In the ACCORD trial, for participants with DM, fenofibrate plus simvastatin 40mg exhibited a 31% reduction in CVEs in the subgroup with baseline high TG and low HDL-C [9].

In fact, more attention has recently been paid to the clinical characters in the early phase of impaired glucose metabolism for the prevention of DM. Pre-DM was an intermediate state between NGR and DM and with high predisposition to develop DM. This metabolic condition was often reversible. The rate of individuals with Pre-DM was almost three times higher than that of DM worldwide and in China (35.7% vs.10.9% in China) [25,30]. The prevalence of Pre-DM and CVEs risk have long been debating. There were different cut-off points in the various definitions to diagnose pre-DM. Studies and meta-analysis using similar blood glucose and HbA1c cut-offs according to 2003 ADA guideline also had different results [31-32]. In our study population, as previously reported, the predictive value of Pre-DM for CVEs was less significant, which was also consistent with studies conducted by Liu et al and Qiu et al [14,

33]. In the present study, 21.8%, 26.6% and 31.2% of patients had AD in NGR, Pre-DM and DM groups. Both Pre-DM and DM groups had higher rate of AD than NGR group. As the main findings of our study, stable CAD patients with Pre-DM plus AD had higher GS and increased risk of CVEs while no statistically significant difference were observed between Pre-DM plus Non-AD and NGR plus Non-AD groups. Therefore, similar attention should be given to patients with Pre-DM and DM when they were with AD.

The present study had several virtues compared with previous published reports. Very few studies have evaluated the differences of coronary severity and outcomes according to both status of glucose metabolism and AD, especially in those with stable CAD. In addition, previous studies were also limited by the fact that the risk of high TG and/ or low HDL-C levels were analyzed separately within DM or NGR population, neglecting of the potential high risk which was caused by the interaction of lipid and glucose. Moreover, there were no such studies about the impacts of AD on cardiovascular outcomes in CAD patients with Pre-DM. Apparently, a large sample size of angiography-proven CAD patients with high prevalence of DM and pre-DM were enrolled in the present study. Hard endpoints containing nonfatal strokes, nonfatal MI, and cardiovascular mortality were also observed during a relatively long follow-up period. Thereby, our study provided important information regarding dyslipidemia, glucose metabolism status and outcome.

Nevertheless, there are still several limitations in the present study. Firstly, this is a single center study among Chinses patients with stable CAD. Secondly, we measured TG, HDL-C and glucose metabolism status only at the baseline. The follow-up levels of TG/HDL-C may also be clinically significant. According to previous study, during the follow-up period, a small proportion of subjects with Pre-DM may develop DM each year [34]. The increased CAD severity and CVEs may be overestimated in the Pre-DM group. Thirdly, we did not assess all metabolic factors and parameters about insulin resistance due to the features of patients in our

study. Fourthly， even if AD plus NGR group did not present increased CVEs risk, there is possibility that the result missed the statistical significance level due to smaller number of subjects. Hence, further studies with larger sample size may be needed.

In conclusion, in our large sample size with long-term follow-up study, data indicated that the Pre-DM and DM patients with AD had significantly higher risk of CVEs, suggesting that treatment and lifestyle management towards AD in Pre-DM and DM patients may also be crucial for improving clinical outcomes.

Contributors

Study concept and design: Professor Jian-Jun-Li, Dr Ying Gao and Dr Jing-Lu Jin. Acquisition of data: Prof. Jian-Jun-Li, Dr Ye-Xuan Cao and Dr Jing-Lu Jin. Analysis and interpretation of data: Dr Ying Gao and Dr Jing-Lu Jin. Drafting of the manuscript: Dr Jing-Lu Jin. Critical revision of the manuscript for important intellectual content: Professor Jian-Jun-Li. Statistical analysis: Dr Jing-Lu Jin. Obtained funding: Professor Jian-Jun-Li and Dr Ying Gao. Administrative, technical or material support: Drs Li-Guo Wu, Xiang-Dong You, Yuan-Lin Guo, Na-Qiong Wu, Cheng-Gang Zhu, Hui-Hui Liu, Rui-Xia Xu and Miss Jing Sun and Qian Dong. Study supervision: Prof Jian-Jun Li.

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Competing interests

None declared.

Patient consent

Obtained.

Ethics approval

The study was performed according to the Declaration of Helsinki, and the hospital ethics review board (Fuwai Hospital and National Center for Cardiovascular Diseases, Beijing, China) approved the protocol.

Data sharing statement

The technical appendix, statistical code and data set are available from the corresponding author.

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Figure Legends

Figure 1 Flowchart of the study

Figure 2 Coronary severity in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia * for $p<0.05$

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

Tables

Table 1. Baseline characteristics of the participants according to different glucose metabolism

	Total n=3057	NGR n=610	Pre-DM n=1370	DM n=1077	P
Clinical factors					
Age, years	58.5±9.8	55.5±10.0	58.8±9.4	59.9±9.8	<0.001
Male, n (%)	2149(70.3)	438(71.8)	956(69.8)	755(70.1)	0.651
BMI (kg/m^2)	25.6±3.2	25.0±3.0	25.5±3.2	26.1±3.2	<0.001
HT, n (%)	1904(62.3)	339(55.6)	804(58.7)	761(70.7)	<0.001
Family history of CAD	494(16.2)	112(18.4)	221(16.1)	161(14.9)	0.188
Current Smoker, n (%)	1580(51.7)	307(50.3)	714(52.1)	559(51.7)	0.751
Drinking, n (%)	764(25.0)	171(28.0)	333(24.3)	260(24.1)	0.152
Revascularization, n (%)	2182(71.4)	432(70.8)	992(72.4)	758(70.4)	0.514
Laboratory factors					
Glucose (mmol/L)	5.6±1.6	4.7±0.4	5.1±0.6	6.7±2.1	<0.001
HbA1c (%)	6.3±1.1	5.4±0.2	6.0±0.2	7.3±1.2	<0.001
Creatinine (μmol)	73.6±14.1	73.5±14.1	73.3±13.1	74.1±15.2	0.335
hsCRP (μmol/L)	1.5(0.8-2.9)	1.1(0.6-2.2)	1.5(0.8-2.9)	1.7(0.9-3.3)	<0.001
TC (mmol/L)	4.13±1.02	4.00±1.00	4.18±1.00	4.13±1.05	0.001
HDL-C (mmol/L)	1.07±0.28	1.10±0.30	1.09±0.27	1.05±0.27	<0.001
LDL-C (mmol/L)	2.46±0.88	2.37±0.86	2.51±0.87	2.46±0.89	0.003
TG (mmol/L)	1.48(1.09-2.03)	1.38(1.00-1.85)	1.44(1.09-1.98)	1.59(1.17-2.18)	<0.001
LVEF (%)	63.3±7.9	64.0±6.9	63.2±8.4	63.0±7.8	0.026
GS	26(9-44)	24(8-34)	24(8-40)	32(12-56)	<0.001
Prior Medications					
Aspirin, n (%)	2657(86.9)	519(85.1)	1203(87.8)	935(86.8)	0.249
Statins, n (%)	2193(71.7)	423(69.3)	978(71.4)	792(73.5)	0.171
ACEIs/ARBs, n (%)	798(26.1)	149(24.4)	364(26.6)	285(26.5)	0.572
β-blockers, n (%)	1598(52.3)	294(48.2)	721(52.6)	573(53.6)	0.112
Antidiabetic drug					
OADs, n(%)	648(21.2)	-	-	648(60.2)	
Insulin, n(%)	382(12.5)	-	-	382(35.5)	

Data were expressed as mean ± SD, median with 25th and 75th percentile or n (%).

BMI: body mass index; HT: hypertension; CAD: coronary artery disease; HbA1c: haemoglobin A1c; hsCRP: high sensitive C-reactive protein; TC: total cholesterol; TG: triglyceride; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; LVEF: left ventricular ejection fraction;

GS:gensini score; ACEIs: angiotensin-converting enzymes; ARBs: angiotensin receptor blocker; OADs: oral antidiabetic drug.

Table 2. Cox regression models in predicting cardiovascular events according to different glucose metabolism

Diabetic status (n, events/subjects)	HR (95%CI)		
	Unadjusted model	model 1	model 2
NGR (46/610)	Ref	Ref	Ref
Pre-DM (135/1379)	1.31 (0.94-1.83)	1.29 (0.92-1.81)	1.25 (0.89-1.76)
DM (127/1077)	*1.56 (1.11-2.19)	*1.53 (1.09-2.15)	*1.45 (1.02-2.05)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus;

Model 1 adjusted for age and sex; model 2 adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease, Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, high density lipoprotein cholesterol, triglyceride, high sensitive C-reactive protein, and baseline statins;

Table 3. Cox Regression Models in Predicting cardiovascular events according to different status of glucose metabolism and atherogenic dyslipidemia

DM/AD category	Events/Subjects 308/3057	HR (95%CI) Crude Model	HR (95%CI) Adjusted Model
NGR, Non-AD	31/477	Ref	Ref
Pre-DM, Non-AD	92/1005	1.42 (0.94-2.13)	1.40 (0.92-2.10)
DM, Non-AD	84/741	*1.75 (1.16-2.64)	*1.68 (1.11-2.56)
NGR, AD	15/133	1.74 (0.94-3.22)	1.74 (0.94-3.23)
Pre-DM, AD	43//365	*1.81 (1.14-2.88)	*1.76 (1.10-2.80)
DM, AD	43/336	*1.95(1.23-3.09)	*1.87 (1.17-2.98)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; AD: atherogenic dyslipidemia;

Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease, Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, high sensitive C-reactive protein, and baseline statins;

Figure legends

Figure 1 Flowchart of the study. CAD, coronary artery disease; ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; NGR: normal glucose regulation; Pre-DM, pre-diabetes mellitus; DM, diabetes mellitus.

Figure 2 Coronary severity in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

* for $p<0.05$; ** for $p<0.01$

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to **a.** different glucose metabolism; **b.** different status of glucose metabolism and atherogenic dyslipidemia

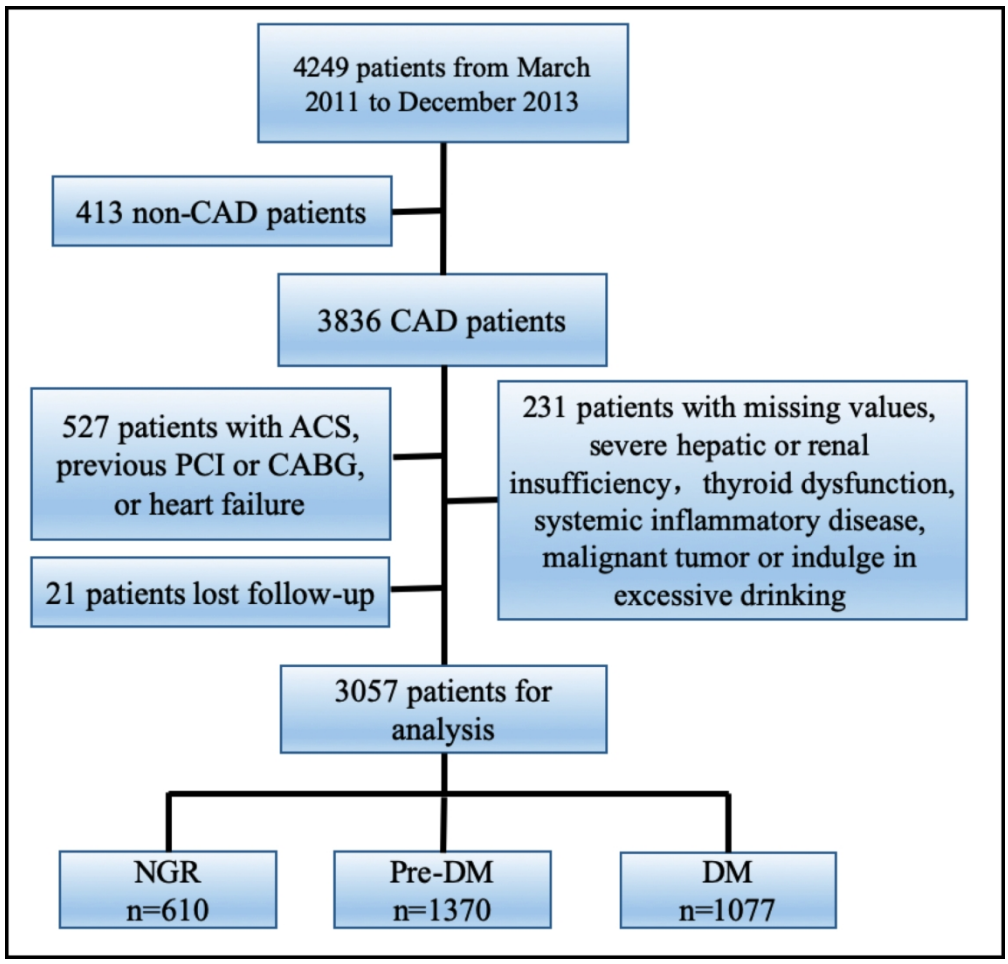

Figure 1 Flowchart of the study.

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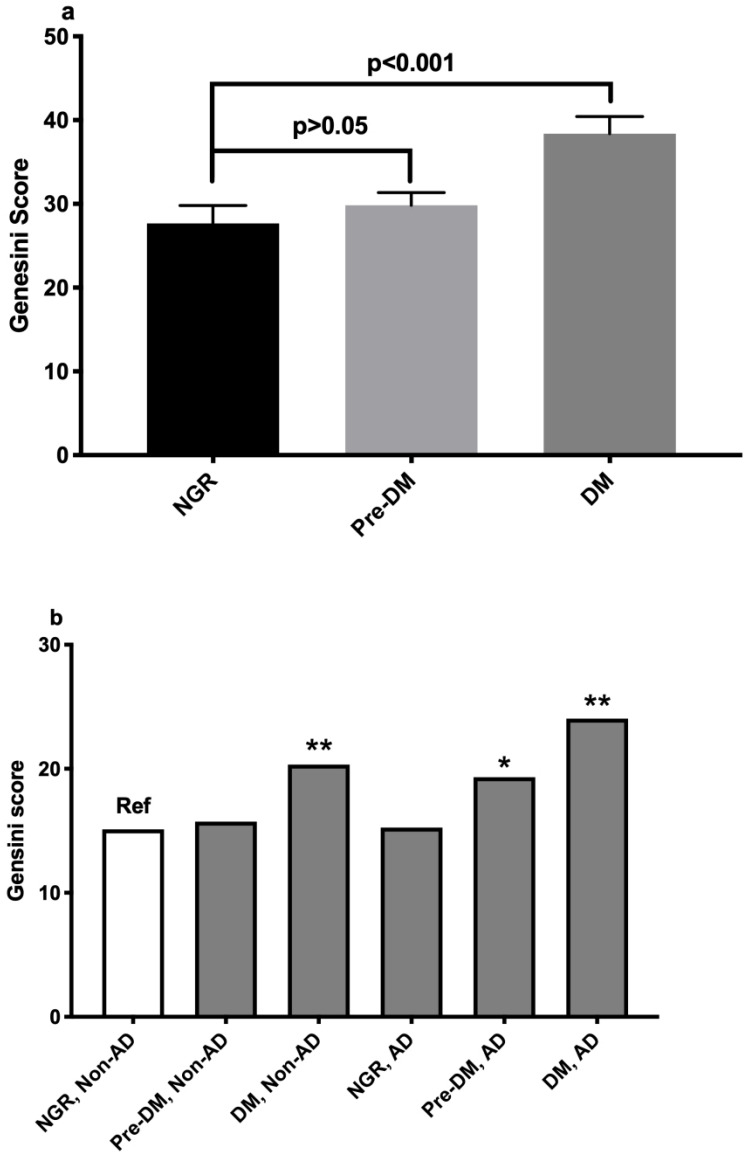

Figure 2 Coronary severity in participants according to a. different glucose metabolism; b. different status of glucose metabolism and atherogenic dyslipidemia * for p<0.05; ** for p<0.01

174x269mm (300 x 300 DPI)

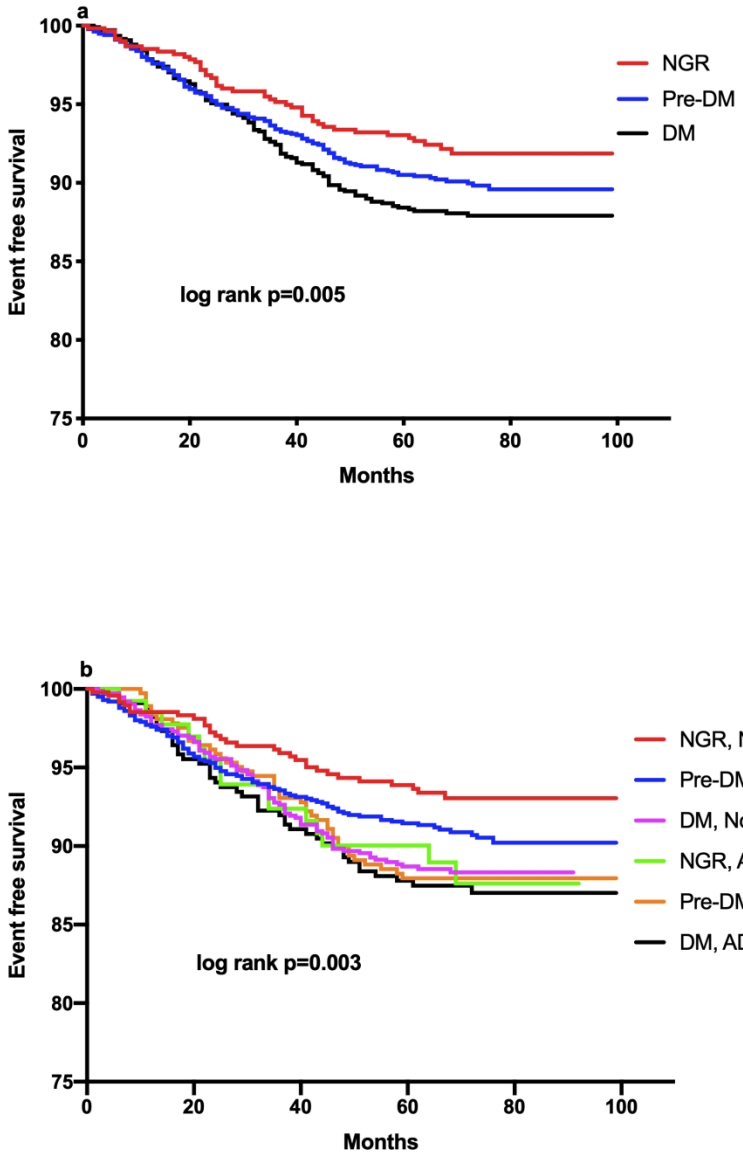

Figure 3 Kaplan-Meier curves and log-rank tests for cardiovascular events in participants according to a. different glucose metabolism; b. different status of glucose metabolism and atherogenic dyslipidemia

183x250mm (300 x 300 DPI)

Supplemental Data.

Supplemental Table S1 Logistic regression analysis regarding the association between glucose metabolism status and high Gensini score (median as cut-off)

	OR (95%CI)	
DM category	**Crude Model**	**Adjusted Model**
NGR	Ref	Ref
Pre-DM	1.03 (0.85-1.24)	0.97(0.80-1.18)
DM	*1.55 (1.27-1.90)	*1.42 (1.16-1.75)

* for $p<0.05$

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease. Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, triglyceride, high density lipoprotein cholesterol, high sensitive C-reactive protein and baseline statins;

Supplemental Table S2 Logistic regression analysis regarding the association between combined status of glucose metabolism status and stherogenic dyslipidemia and high Gensini Score (median as cut-off)

	OR (95%CI)	
DM/AD category	**Crude Model**	**Adjusted Model**
NGR, Non-AD	Ref	Ref
Pre-DM, Non-AD	0.92 (0.74-1.15)	0.89 (0.71-1.11)
DM, Non-AD	*1.51(1.20-1.90)	*1.43(1.13-1.81)
NGR, AD	1.01(0.69-1.48)	1.01(0.68-1.49)
Pre-DM, AD	*1.39(1.06-1.83)	*1.37(1.04-1.81)
DM, AD	*1.67(1.26-2.21)	*1.64 (1.23-2.19)

NGR: normal glucose regulation; Pre-DM: pre-diabetes mellitus; DM: diabetes mellitus; AD: atherogenic dyslipidemia;

Model adjusted for age, sex, body mass index, smoking, hypertension, family history of coronary artery disease. Gensini score, left ventricular ejection fraction, low density lipoprotein cholesterol, and high sensitive C-reactive protein, and baseline statins;

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	7
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	6-7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6-7
		(c) Summarise follow-up time (eg, average and total amount)	6-7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	7 6-7 7-8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8-9
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.