

# BMJ Open Atherogenic dyslipidaemia and cardiovascular events in patients with diabetes or pre-diabetes and stable coronary artery disease: a prospective, cohort study

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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) dyslipidaemia 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 three groups according to different glucose metabolism status. Atherogenic dyslipidaemia (AD) was defined as TG  $\geq$ 1.7 mmol/L and HDL-C  $<$ 1.0 mmol/L for men or  $<$ 1.3 mmol/L for women. The patients were further classified into six 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 normal glucose regulation (NGR) and pre-diabetes (pre-DM) groups (HR: 1.25, 95% CI 0.89 to 1.76) while DM group presented 1.45-fold higher risk of CVEs (HR: 1.45, 95% CI 1.02 to 2.05). When the participants were categorised 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 to 2.80 and HR: 1.87, 95% CI 1.17 to 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.

## INTRODUCTION

Dyslipidaemia 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).<sup>1</sup> Moreover,

## Strengths and limitations of this study

- This study fills the gap of the current knowledge on the predictive value of atherogenic dyslipidaemia 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 dyslipidaemia on outcomes in such patients.
- This is a single centre, observational study among Chinese patients with stable coronary artery disease (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 patients with CAD and subjects in randomised clinical trials.

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.<sup>2-4</sup> It has been demonstrated in large-scale clinical trials that hypertriglyceridaemia was associated with increased cardiovascular events (CVEs).<sup>5</sup> 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 Randomised Evaluation of the Effects of Anacetrapib through Lipid-modification study but it was not clear whether the risk reduction was attributed to the increase in HDL-C.<sup>6</sup> Type 2 diabetes mellitus (T2DM) is also one of the major risk factors of CVD.<sup>7</sup> Atherogenic dyslipidaemia (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 patients with DM.<sup>8</sup> In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, patients with a combination of high baseline TG ( $\geq 204$  mg/dL, highest tertile) and low baseline HDL-C ( $\leq 34$  mg/dL, lowest tertile) showed possible benefit from fenofibrate plus simvastatin therapy compared with simvastatin alone.<sup>9</sup> Standards of medical care in diabetes from American Diabetes Association (ADA) also recommended intensify lifestyle therapy and optimise glycaemic control for patients with elevated TG levels and/or low HDL cholesterol.<sup>10</sup>

Pre-diabetes (pre-DM) is an abnormal glucose regulation status with high predisposition to developing T2DM. Pre-DM subjects had similar lipid profile as patients with DM. However, the prognosis of patients with pre-DM 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

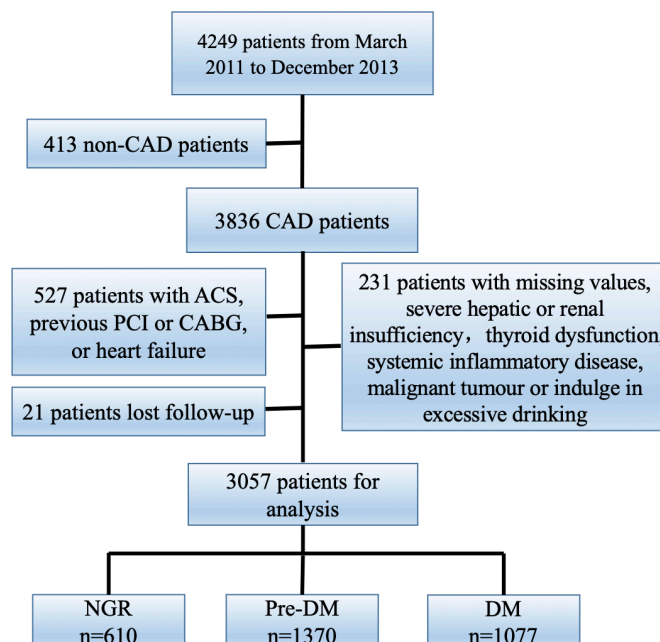
### Study design and participants

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 (figure 1). As reported in detail previously,<sup>11 12</sup> 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.<sup>13</sup> Patients who were without DM or pre-DM were defined as normal glucose regulation (NGR, fasting plasma glucose  $< 5.6$  and haemoglobin A1c (HbA1c) level  $< 5.7\%$ ). AD was defined as TG  $\geq 1.7$  mmol/L and HDL-C  $< 1.0$  mmol/L for men or  $< 1.3$  mmol/L for women. Hypertension was defined as a self-reported hypertension, currently taking antihypertensive drugs or recorded systolic blood pressure (SBP)  $\geq 140$  mm Hg and/or diastolic blood pressure (DBP)  $\geq 90$  mm Hg 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 hours fasting. Concentrations of total cholesterol (TC), TG, LDL-C, HDL-C were measured using automatic biochemistry analyser (Hitachi



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

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 three experienced interventional cardiologists according to our previous studies.<sup>14</sup> The Gensini score (GS) was calculated as previously described.<sup>15</sup>

### Statistical analysis

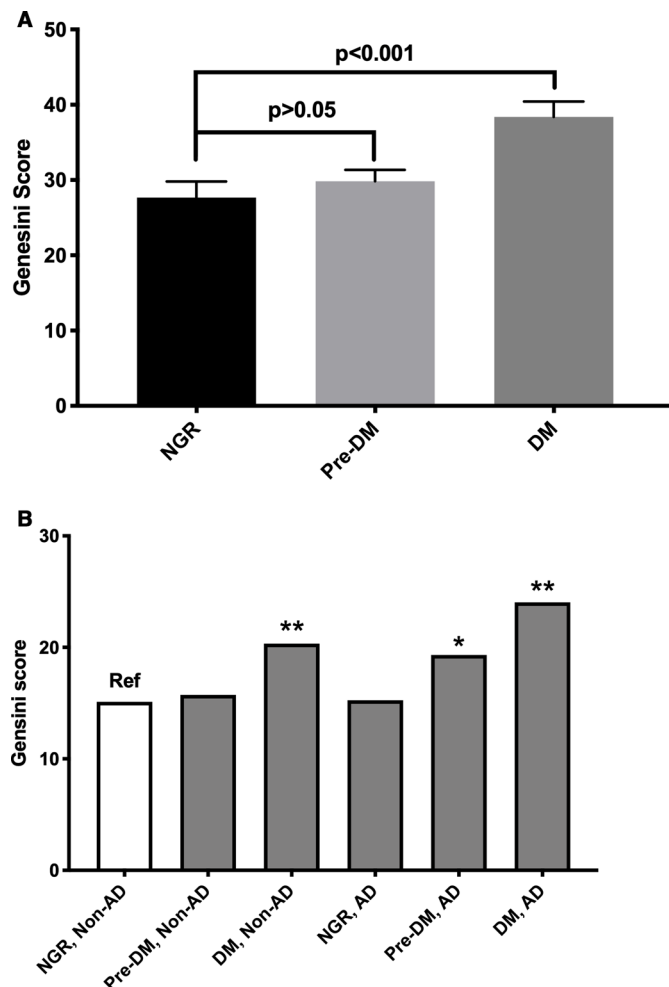
The values were expressed as the mean $\pm$ SD or median (Q1–Q3 quartiles) for the continuous variables and the number (percentage) for the categorical variables. The Kolmogorov-Smirnov test was used to test the distribution pattern. The differences of clinical characteristics between groups were analysed using the Student's t-test, analysis of variance or non-parametric test,  $\chi^2$  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 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 V.21.0 software.

**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 value
<b>Clinical factors</b>					
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 <sup>2</sup> )	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
Revascularisation, n (%)	2182 (71.4)	432 (70.8)	992 (72.4)	758 (70.4)	0.514
<b>Laboratory factors</b>					
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
<b>Prior medications</b>					
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
<b>Antidiabetic drug</b>					
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 (%).

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



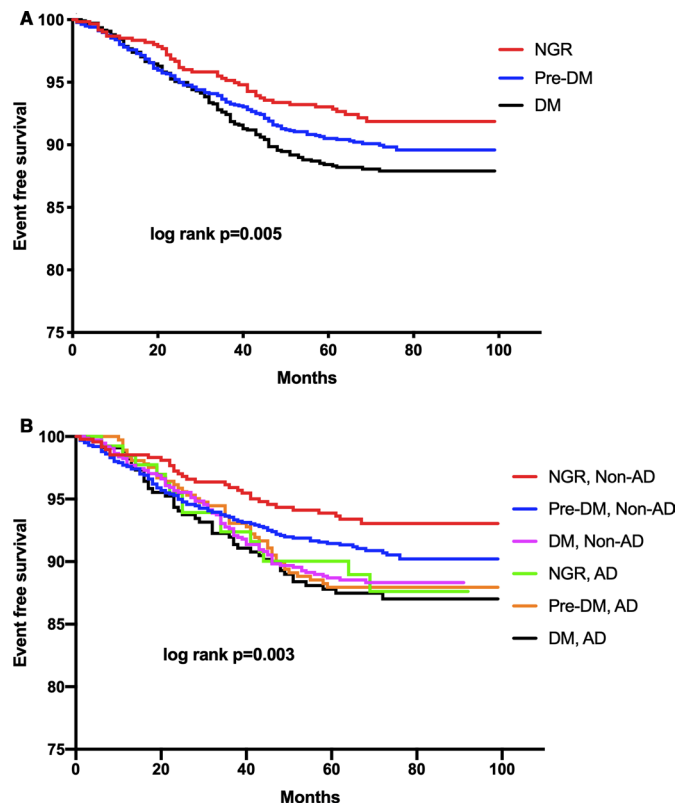
**Figure 2** Coronary severity in participants according to (A) different glucose metabolism; (B) different status of glucose metabolism and atherogenic dyslipidaemia. \* $p < 0.05$ ; \*\* $p < 0.01$ . AD, atherogenic dyslipidaemia; DM, diabetes mellitus; NGR: normal glucose regulation.

### 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 [figure 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 ( $p > 0.05$ ).



**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 dyslipidaemia. AD, atherogenic dyslipidaemia; DM, diabetes mellitus; NGR, normal glucose regulation.

The coronary severity was compared among different status of glucose metabolism. As shown in [figure 2A,B](#), 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 online 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  $p < 0.05$ , online supplemental table S2).

Over a median follow-up time of 6.1 years (5.1–7.5 years), 308 CVEs occurred, including 112 cardiovascular deaths, 73 non-fatal MI and 123 had non-fatal 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 ([figure 3A](#)), DM subjects had the highest event rate among the three groups ( $p < 0.05$ ) while there



**Table 3** Cox regression models in predicting cardiovascular events according to different status of glucose metabolism and atherogenic dyslipidaemia

DM/AD category	HR (95% CI)		
	Events/subjects 308/3057	Crude model	Adjusted model
NGR, non-AD	31/477	Ref	Ref
Pre-DM, non-AD	92/1005	1.42 (0.94 to 2.13)	1.40 (0.92 to 2.10)
DM, non-AD	84/741	*1.75 (1.16 to 2.64)	*1.68 (1.11 to 2.56)
NGR, AD	15/133	1.74 (0.94 to 3.22)	1.74 (0.94 to 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)

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.

\* $p < 0.05$ .

AD, atherogenic dyslipidaemia; DM, diabetes mellitus; NGR, normal glucose regulation; pre-DM, pre-diabetes mellitus.

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, [figure 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% CI 1.02 to 2.05,  $p < 0.05$ ). The GS was also associated with CVEs (HR: 1.004, 95% CI 1.001 to 1.008,  $p < 0.05$ ). Additional adjustment for confounding variables including GS 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 1.68-fold (95% CI 1.11 to 2.56), 1.76-fold (95% CI 1.10 to 2.80) and 1.87-fold (95% CI 1.17 to 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.<sup>16</sup> In this study, we investigated the impact of AD on cardiovascular outcomes in stable, angiography-proven patients with CAD 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 categorised 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, 41.8% patients had high TG and 31.9% patients had low HDL-C among Chinese population.<sup>17</sup> Additionally, studies about reducing CVD risk by lowering TG and raising HDL-C had inconsistent results.<sup>6,9</sup> For example, fibrates did not have conclusive effect in ASCVD risk reduction in ACCORD trials while patients who received 2 g of icosapent ethyl two times per day had lower risk of ischaemic events in Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.<sup>9,18</sup> However, in randomised controlled trials, cholesteryl ester transfer protein inhibitors, which could increase plasma HDL-C, failed to reduce CVEs rates.<sup>9,19–21</sup> In the meanwhile, Mendelian analysis involving about 20 000 MI individuals and

**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 to 1.83)	1.29 (0.92 to 1.81)	1.25 (0.89 to 1.76)
DM (127/1077)	*1.56 (1.11 to 2.19)	*1.53 (1.09 to 2.15)	*1.45 (1.02 to 2.05)

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.

\* $p < 0.05$ .

DM, diabetes mellitus; NGR, normal glucose regulation; pre-DM, pre-diabetes mellitus.

50 000 controls demonstrated that 1 SD increase in TG levels was associated with 54% increased risk of MI.<sup>22</sup> In contrast, no such association was found for patients with low baseline levels of HDL-C.<sup>3</sup> 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.<sup>23</sup> Of noted, patients who were with obesity, insulin resistance or other metabolic abnormalities had higher prevalence of high TG and/or low HDL-C.<sup>24</sup>

DM was the most common metabolic disease in the 21st century. Approximately 415 million adults were with T2DM worldwide.<sup>25</sup> Prevalence of total diagnosed and undiagnosed diabetes in China reached 10.9% in 2013.<sup>26</sup> What is more, CAD was a common comorbidity in patients with DM. According to previous studies, patients with DM 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 ischaemic stroke.<sup>27 28</sup> 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)-hyperlipoproteinaemia.<sup>14 29</sup> 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.<sup>8</sup> In a large cohort of 28 318 DM subjects, increased CAD risk was observed in both men and women with AD.<sup>16</sup> In the ACCORD trial, for participants with DM, fenofibrate plus simvastatin 40 mg exhibited a 31% reduction in CVEs in the subgroup with baseline high TG and low HDL-C.<sup>9</sup>

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).<sup>25 30</sup> 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.<sup>31 32</sup> 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*.<sup>14 33</sup> 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 patients with CAD and 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 analysed 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 patients with CAD and pre-DM. Apparently, a large sample size of angiography-proven patients with CAD with high prevalence of DM and pre-DM were enrolled in the present study. Hard endpoints containing non-fatal strokes, non-fatal MI, and cardiovascular mortality were also observed during a relatively long follow-up period. Thereby, our study provided important information regarding dyslipidaemia, glucose metabolism status and outcome.

Nevertheless, there are still several limitations in the present study. First, this is a single centre study among Chinese patients with stable CAD. Second, 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.<sup>34</sup> The increased CAD severity and CVEs may be overestimated in the pre-DM group. Third, we did not assess all metabolic factors and parameters about insulin resistance due to the features of patients in our study. Fourth, 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 patients with pre-DM and DM with AD had significantly higher risk of CVEs, suggesting that treatment and lifestyle management towards AD in patients with pre-DM and DM may also be crucial for improving clinical outcomes.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**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.

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**Data availability statement** Data are available upon reasonable request. The technical appendix, statistical code and data set are available from the corresponding author.

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