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Serum triglyceride, high-density lipoprotein cholesterol, apolipoprotein B and coronary heart disease in a Chinese population undergoing coronary angiography

Short title: Hypertriglyceridemia and low HDL-C.

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Abstract

Background Increased serum triglyceride and apolipoprotein B (apoB) levels and decreased high-density lipoprotein cholesterol (HDL-C) levels are risk factors for cardiovascular diseases. The major types of dyslipidemia in Chinese population are hypertriglyceridemia and low HDL-C.

Objective This study aimed to evaluate the effect of HDL-C, triglyceride, and apoB levels on the risk of coronary heart disease (CHD) in a Chinese population undergoing coronary angiography.

Methods This was a cross-sectional study. 1941 consecutive patients who were referred to coronary angiography for the evaluation of suspected CHD were recruited. Lipid parameters were measured after an overnight fast. Patients were diagnosed with CHD and without CHD based on the findings of the coronary angiography.

Results There were 1363 angiography confirmed CHD patients and 578 non-CHD patients. In non-statin users, the major types of dyslipidemia were hypertriglyceridemia combined with low HDL-C, isolated low HDL-C, and isolated hypertriglyceridemia, accounting for 21.60%, 19.70% and 14.99%, respectively. In statin users, a low to moderate-intensity statin was effective in lowering low-density lipoprotein cholesterol (LDL-C). The proportion of reaching a LDL-C goal of less than 2.6mmol/L and less than 1.8mmol/L in statin users was 83.20% and 55.19%, respectively. In non-statin users, the triglyceride and apoB levels were higher and the HDL-C levels were lower in CHD patients compared to non-CHD patients after the adjustment of age, sex, BMI, diabetes, smoking and alcohol-drinking (P = 0.002, 0.007, and 0.005, respectively). After adjusting for age, sex, BMI, diabetes, hypertension, smoking and

alcohol-drinking, the quartiles of triglyceride, HDL-C and apoB were associated with CHD (P for trend = 0.001, 0.005, and 0.003, respectively).

Conclusion Serum triglyceride, HDL-C and apoB levels were independently associated with CHD in a Chinese population undergoing coronary angiography with a relatively low level of LDL-C and a high prevalence of hypertriglyceridemia and low HDL-C.

Keywords triglyceride, apolipoprotein B, high-density lipoprotein cholesterol, coronary heart disease, statin

Background

Interventional trials using statins to lower low-density lipoprotein cholesterol (LDL-C) have established the causal role of LDL-C in coronary heart disease (CHD)[1, 2]. However, in all the statin trials, there remains a substantial residual risk in the treated group. The residual risk may relate to a low baseline high-density lipoprotein cholesterol (HDL-C) and a high baseline triglyceride levels[3-5]. In fact, HDL-C has been consistently shown as a protective factor against cardiovascular disease (CVD) in population studies. In the Framingham Heart Study, the major potent lipid risk factor of CHD was HDL-C, while LDL-C had a weaker association with the incidence of CHD[6]. In an analysis of more than 300,000 people from 68 long-term prospective studies, each increase of 15 mg/dL HDL-C was associated with a decrease of 22% in the risk of CHD[7]. Moreover, the association of HDL-C with CVD was maintained at very low levels of LDL-C. The post hoc analysis of the Treating to New Targets study concluded that HDL-C levels were predictive of major cardiovascular events in patients treated with statins, and this relationship was also observed among patients with LDL-C levels below 70 mg/dL[3]. The inverse relationship between HDL-C and coronary risk persisted even among patients with LDL-C levels below 60 mg/dL in another study[4]. It should be noted that recent studies using Mendelian randomization methods suggested that the relationship between HDL-C and CHD risk is null[8-10]. Even so, facts about the association of HDL-C with CHD from observational studies should not be neglected. HDL-C remains a useful biomarker unless an easily available functional HDL biomarker is developed, and the role of HDL-C in CHD risk prediction deserves to be studied more extensively.

Observational studies also indicate an unambiguous association of triglyceride levels with

CHD. In 29 western prospective studies including 262,525 participants, raised circulating triglyceride levels were associated with increased CHD risk after adjustment for established coronary risk factors, and the adjusted odds ratio was 1.72 (95% CI, 1.56-1.90) in a comparison of individuals in the top third with those in the bottom third of usual log-triglyceride values[11]. A meta-analysis of 26 prospective studies conducted in the Asia-Pacific region also indicated serum triglyceride levels were an important and independent predictor of CHD during 796,671 person-years of follow-up among 96,224 individuals[12]. In a recent study, fasting triglycerides predict long-term and short-term cardiovascular risk among patients with ACS treated effectively with statins[5]. More importantly, recent genetic studies support a causal relationship between triglycerides and CHD risk using a Mendelian randomization design[9]. As triglycerides per se may not cause cardiovascular disease directly, remnant cholesterol in triglyceride-rich lipoproteins is more likely to be the causal factor[7, 13]. By using a Mendelian randomization design, a 1mmol/L increase of non-fasting remnant cholesterol was associated with a 2.8-fold causal risk for ischemic heart disease in a total of 73,513 subjects from Copenhagen[8].

As the components of metabolic syndrome, hypertriglyceridemia and low HDL-C are tightly associated with insulin resistance[14-16]. Progressive insulin resistance was associated with a decrease in average low-density lipoprotein (LDL) size as a result of an increase in small and a reduction in large LDL subclasses, and an increase in overall LDL particle concentration, which together led to a normal or modestly elevated LDL-C levels[16]. Apolipoprotein B (apoB) represents the number of the entire spectrum of atherogenic lipoprotein particles in the circulation, including LDL, intermediate-density lipoprotein (IDL),

lipoprotein (a) and very low-density lipoprotein (VLDL)[17]. Discordance analysis demonstrated that atherogenic particle numbers, estimated as apoB concentration or LDL particle number, are better markers of cardiovascular risk than LDL-C or non-high-density lipoprotein cholesterol (nonHDL-C)[18-21]. In a recent report of the Framingham Heart Study, apoB improves risk assessment of future CHD events beyond LDL-C or nonHDL-C[22]. These studies support that coronary risk is more closely associated with the number of atherogenic apoB particles than the mass of cholesterol within them.

Several studies have shown that the major types of dyslipidemia in Chinese population are hypertriglyceridemia and low HDL-C, while the prevalence of high cholesterol is low[23-25]. However, the effect of serum HDL-C and triglyceride levels on the risk of CHD is still controversial in Chinese population[26-28]. A community-based cohort study in Taiwanese found that apoB concentration was a better predictor of the risk of CHD than LDL-C and nonHDL-C[29]. There is no study directly examining the effect of apoB concentration on CHD in Chinese from the mainland of China. Therefore, this study aimed to evaluate the effect of HDL-C, triglyceride, and apoB levels on the risk of CHD in a Chinese population undergoing coronary angiography.

Methods

Study population

Between March 2013 and November 2013, we recruited consecutive patients who were referred to coronary angiography for the evaluation of suspected CHD in the Cardiology Department of Zhongshan Hospital in Shanghai. The patients with suspected CHD had chest pain or dyspnea symptoms, and were transferred to Zhongshan hospital for further diagnosis.

They were first evaluated by routine or dynamic electrocardiogram or coronary computed tomography angiography or stress myocardial perfusion imaging or exercise treadmill test in the outpatient department. They were hospitalized to have coronary angiography for a definite diagnosis if one of these tests was abnormal. Patients with incomplete data or whose serum triglyceride > 4.5mmol/L were excluded. We also excluded patients who used non-statin lipid-lowering medications. Finally, 1941 patients were enrolled in this study. The Ethics Committee of Zhongshan Hospital of Fudan University approved this study, and all participants gave written informed consent.

Clinical assessment

BMI was calculated as weight (kilograms)/height squared (meter^2). Waist circumference was measured midway between the lower rib margin and the iliac crest in a standing position. Hypertension was defined by the following criteria: diagnosis of hypertension made previously by a physician or a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90mmHg or treatment with antihypertensive medications. Diabetes mellitus was defined by the following criteria: diagnosis of diabetes made previously by a physician or a fasting plasma glucose ≥7mmol/L, or a 2-hour postprandial glucose ≥11.1mmol/L, or a glycosylated hemoglobin (HbA1c) ≥6.5%, or use of insulin or oral hypoglycemic agents. Dyslipidemia was defined as a serum LDL-C ≥3.37mmol/L, a triglyceride ≥1.7mmol/L, or a HDL-C <1.04mmol/L[30]. Metabolic syndrome was defined as having three or more components as the following: 1) waist circumference > 90cm in males and >85cm in females; 2) serum triglyceride ≥1.7mmol/L; 3) serum HDL-C <1.04mmol/L; 4) blood pressure ≥130/85mmHg; 5) fasting plasma glucose ≥ 6.1mmol/L, or 2-hour plasma glucose during an

oral glucose tolerance test ≥ 7.8mmol/L, or a history of diabetes[30]. Smoking state was defined as never smoking, current smoking, or ever smoking. Alcohol drinking state was defined as never drinking, current drinking, or ever drinking. Statin use was documented as current use or no use. The statin species and statin dose were recorded.

Laboratory assays

Venous blood samples were collected in the morning after an overnight fast for at least 12 hours before angiography was performed. Fasting glucose, 2-hour postprandial glucose, triglyceride, total cholesterol, HDL-C, apolipoprotein A-I (apoAI), apoB were determined by enzymatic methods (Roche Diagnostics, Basel, Switzerland) using Hitachi 7600 biochemistry autoanalyzer (Hitachi High-Technologies Crop., Tokyo, Japan). LDL-C was calculated using the Friedewald formula[31]. NonHDL-C was calculated as total cholesterol minus HDL-C. Remnant cholesterol was calculated as total cholesterol minus HDL-C minus LDL-C. HbA1c was measured by high performance liquid chromatography using the Bio-Rad Variant II analyzer (Bio-Rad Laboratories, Hercules, CA, USA). Serum insulin were measured using electrochemiluminescence immunoassay by Mobular E170 automatic electrochemiluminescence analyzer (Roche Diagnostics Ltd., Shanghai, China) (coefficient of variation <5.0%). Homeostasis model assessment of insulin resistance (HOMA-IR) index was used to estimate insulin sensitivity[32].

Angiographic analysis

Two experienced cardiologists who were blinded to the study protocol carried out the angiographic analysis, and a percentage stenosis was given to the major epicardial arteries and sub-branches. Based on the findings of the coronary angiography, patients were

diagnosed with CHD (≥50% stenosis in ≥1 coronary vessel) and without CHD.

Statistical analysis

Continuous variables were expressed as means ± SEM or median (interquartile range) and categorical variables as percentages. The independent sample *t* test and the x^2 test were used to compare differences of continuous variables and categorical variables between groups, rspectively. General linear model was used to examine the differences of lipid parameters between patients with CHD and patients without CHD. We divided the distribution of lipid parameters into quartiles. Logistic regression analysis were used to investigate the independent association of lipid parameters with CHD, and the adjusted odds ratios (ORs) were calculated in relation to each quartile increase of lipids concentrations. Non-normally distributed values were natural log-transformed before analysis. All statistical analyses were performed using SPSS software version 19.0. Statistical tests were two-tailed and p values <0.05 were considered statistical significant.

Results

In the current study, among 1941 participants, 72.5% were men, with a mean age of 61.3 years. There were 1363 angiography confirmed CHD patients and 578 non-CHD patients. The characteristics of the participants were shown in Table 1. Patients with CHD were older, and were more likely to be male, current smokers and current drinkers. The BMI of CHD patients were similar to that of non-CHD patients, but the waist circumference of CHD patients were higher than that of non-CHD patients. Patients with CHD were more likely to have higher fasting glucose, 2-hour postprandial glucose and HbA1c levels, and the proportion of diabetes were also higher. The systolic blood pressure levels and the proportion of hypertension of

CHD patients were higher than that of non-CHD patients. There were more statin users in CHD patients compared with non-CHD patients. The serum HDL-C levels of CHD patients were lower than that of non-CHD patients. The serum triglyceride and remnant cholesterol levels of CHD patients were higher compared with non-CHD patients. There was no significant difference of total cholesterol, LDL-C, non HDL-C, apoA-I and apoB levels between CHD patients and non-CHD patients.

We also compared the characteristics between statin users and non-statin users among the participants (Table 2). Statin users were older, and have lower blood pressure levels. The proportion of current drinkers in statin users was lower. The concentrations of total cholesterol, triglyceride, LDL-C, nonHDL-C, remnant cholesterol and apoB in statin users were lower, while the concentrations of HDL-C and apoA-I were higher compared to non-statin users. There was no significant difference of gender, waist circumference, BMI, plasma glucose, HbA1c, the proportion of diabetes and hypertension, and the smoking state between statin users and non-statin users.

We analyzed the distribution of high LDL-C, hypertriglyceridemia, and low HDL-C in non-statin users. 67% of patients had dyslipidemia, and 33% had normal lipids levels. The major types of dyslipidemia were hypertriglyceridemia combined with low HDL-C, isolated low HDL-C, and isolated hypertriglyceridemia, accounting for 21.60%, 19.70% and 14.99% of non-statin users respectively (Figure 1). Other types including isolated high LDL-C or dyslipidemia with high LDL-C as a component accounted for a small part of non-statin users (10.71%).

Among the statin users, the frequently used statins were atorvastatin, rosuvastatin and

simvastatin as shown in Figure 2A. The mean daily doses for statins were relatively low as shown in Figure 2B. The mean LDL-C level in statin users was 1.88 mmol/L, and the LDL-C level was similar between CHD patients and non-CHD patients (P=0.54) (Figure 2C). The proportion of reaching a LDL-C goal of less than 2.6mmol/L and less than 1.8mmol/L in statin users was 83.20% and 55.19% respectively (Figure 2D). There was no significant difference between CHD patients and non-CHD patients of reaching a LDL-C goal of less than 2.6mmol/L and less than 1.8mmol/L (P=0.56 and 0.44 respectively) (Figure 2D).

We compared the differences of lipids levels between CHD and non-CHD patients in statin users and non-statin users using general linear model. In statin users, after the adjustment of age, sex, BMI, diabetes, smoking and alcohol-drinking, only the nonHDL-C level of CHD patients was higher than that of non-CHD patients (P = 0.03). Total cholesterol, triglyceride, LDL-C, remnant cholesterol, HDL-C, apoB and apoA-I levels had no significant difference between CHD and non-CHD patients (P = 0.11, 0.73, 0.15, 0.75, 0.64, 0.06 and 0.50, respectively). In non-statin users, the triglyceride, remnant cholesterol and apoB levels were higher and the HDL-C levels were lower in CHD patients compared to non-CHD patients after the adjustment of age, sex, BMI, diabetes, smoking and alcohol-drinking (P = 0.002, <0.001, 0.007, and 0.005, respectively), while total cholesterol, LDL-C, nonHDL-C and apoA-I had no significant difference between CHD and non-CHD patients (P = 0.08, 0.21, 0.15, and 0.88, respectively).

We further investigated the association of lipid parameters with CHD (Table 3). Lipid parameters were classified into quartiles, and ORs for CHD were calculated in relation to each quartile increase of lipids concentrations using logistic regression. After adjustment for

age, sex, BMI, diabetes, hypertension, smoking and alcohol-drinking, the quartiles of serum triglyceride, remnant cholesterol and HDL-C were associated with CHD (P for trend = 0.001, <0.001 and 0.005). Although the quartiles of LDL-C were not associated with CHD (P for trend = 0.55), we found significant associations of the quartiles of apoB and nonHDL-C with CHD (P for trend = 0.003 and 0.01). The quartiles of total cholesterol and apoA-I were not associated with CHD (P for trend = 0.15 and 0.79).

To further examine the independent relationship between triglyceride, remnant cholesterol, HDL-C, apoB, nonHDL-C and CHD, we adjusted lipid parameters in the regression models. The quartiles of triglyceride were significantly associated with CHD after additional adjustment of HDL-C and LDL-C (P for trend = 0.008). The quartiles of remnant cholesterol were significantly associated with CHD after additional adjustment of HDL-C and LDL-C (P for trend = 0.003). Although serum triglyceride levels represent the burden of triglyceride-rich lipoproteins, it is the cholesterol content in the triglyceride-rich lipoproteins which is believed to confer atherogenicity[7, 13]. We further examined the independent effect of triglyceride and remnant cholesterol on CHD. If further adjusted for HDL-C, LDL-C and remnant cholesterol, the association of quartiles of triglyceride with CHD became non-significant (P for trend = 0.51). However, if further adjusted for HDL-C, LDL-C and triglyceride, the association of quartiles of remnant cholesterol with CHD remained significant (P for trend = 0.005). The quartiles of HDL-C were significantly associated with CHD after additional adjustment of triglyceride and LDL-C (P for trend = 0.02). However, the relationship between quartiles of nonHDL-C and CHD became non-significant after additional adjustment of triglyceride and HDL-C (P for trend = 0.10). The quartiles of apoB were significantly associated with CHD

after additional adjustment of triglyceride and HDL-C (P for trend = 0.01). If further adjusted triglyceride, HDL-C and LDL-C, the association between apoB and CHD remained significant (P for trend = 0.03).

As the important role of insulin resistance in regulating concentrations of serum triglyceride, HDL-C and apoB, we also evaluated insulin resistance and metabolic syndrome in non-statin users (Figure 3). HOMA-IR was computed in non-statin users without a known history of diabetes. We found that patients with CHD has a higher level of HOMA-IR compared with patients without CHD (1.88 (1.33-2.91) vs. 1.68 (1.11-2.42), P = 0.001) (Figure 3A). In non-statin users, the proportion of metabolic syndrome in CHD patients was higher compared with non-CHD patients (56.17% vs. 40.22%, P < 0.001) (Figure 3B). Consistently, patients with CHD had more components of metabolic syndrome compared with non-CHD patients (P < 0.001) (Figure 3C).

Dicussion

Risk factors for cardiovascular diseases and type 2 diabetes often cluster, including central obesity, insulin resistance, hyperglycemia, dyslipoproteinemia, and hypertension[33]. All this factors are regarded as cardiometabolic risks, which increases the risk of CVD[33]. In our study population, the proportion of diabetes, hypertension, and central obesity was 34%, 68% and 37%, respectively. Therefore, it is a population with multiple cardiometabolic risks. Lipoprotein abnormalities, including elevated triglyceride, low HDL-C, and increased numbers of small dense LDL particles and apoB concentrations, are common findings in subjects with cardiometabolic risks[34]. We found that there was a high prevalence of dyslipidemia in the study population, and the major types of dyslipidemia were

hypertriglyceridemia combined with low HDL-C, isolated low HDL-C, and isolated hypertriglyceridemia. The prevalence of hypercholesterolemia was relatively low in our population. Consistent with our findings, several previous studies in Chinese also demonstrated that the prevalence of hypertriglyceridemia and low HDL-C were much higher than the prevalence of hypercholesterolemia[23-25], suggesting a relatively low levels of LDL-C or total cholesterol in Chinese compared to white people. When adjusting confounding like age, sex, BMI, diabetes, smoking and alcohol-drinking, we found that serum triglyceride and apoB levels were higher, and serum HDL-C levels were lower in CHD patients compared with non-CHD patients in non-statin users. However, there was no difference of serum triglyceride, apoB and HDL-C levels between CHD and non-CHD patients in stain users. The baseline lipids profile may be different between statin users and non-statin users. It is possible that statin users may have higher baseline total cholesterol and LDL-C levels than those non-stain users, thus leading to their treatment with a statin. Another possibility is that the treatment with statins makes the difference of serum triglyceride, apoB and HDL-C between CHD and non-CHD patients insignificant anymore. Our findings suggested that hypertriglyceridemia and low HDL-C, as the major types of dyslipidemia in Chinese population, may be important risk factors for CHD in Chinese population.

Next, we demonstrated that higher serum triglyceride and apoB levels were associated with increased risk of CHD, while higher serum HDL-C levels were protective for CHD. Evidences have shown that elevated levels of triglycerides, low levels of HDL-C may be important cardiovascular risk factors which persists in patients at the LDL-C goal[3-5]. Our study was conducted in a population with a relatively low mean LDL-C concentration of 2.24

mmol/L and a high prevalence of elevated triglyceride and low HDL-C. We found that serum triglyceride and HDL-C concentrations were associated with CHD adjusted for traditional risk factors. More importantly, the association of triglyceride and HDL-C with CHD remained significant after additional adjustment of LDL-C. Although epidemiological studies and genetic studies have demonstrated that high triglyceride was a risk factor of cardiovascular diseases[9, 11, 12], there are still many controversies[7, 35]. In fact, triglyceride per se is not likely to cause atherosclerosis. It is the cholesterol content in the triglyceride-rich lipoproteins which is believed to take part in atherogenicity[13, 36]. However, serum triglyceride levels represent the burden of triglyceride-rich lipoproteins in circulation, and it may serve as a useful marker of triglyceride-rich lipoproteins[13, 36]. In our study, both serum triglyceride and remnant cholesterol in triglyceride-rich lipoproteins were associated with CHD. Moreover, the association of remnant cholesterol with CHD remained significant after adjusting for triglyceride. But the association of triglyceride with CHD became non-significant after adjusting for remnant cholesterol. Therefore, serum triglyceride serves as a useful surrogate marker for remnant cholesterol in triglyceride-rich lipoproteins in risk prediction of cardiovascular diseases. In contrast to triglyceride, HDL is considered an anti-atherogenic and vasculoprotective lipoprotein[37]. Cellular cholesterol efflux activity and anti-oxidative actions are the key mechanisms for the anti-atherogenic function of high-density lipoprotein (HDL)[38].

The observed abnormalities of lipid metabolism in our study are closely associated with insulin resistance. In the background of insulin resistance, hypertriglyceridemia is related to the over-secretion of triglyceride-rich VLDL particles[13, 34]. The exchange of triglyceride in VLDL for cholesterol ester in LDL and HDL produce triglyceride-rich LDL and HDL

particles[13, 34]. Then, these triglyceride-rich LDL and HDL particles are hydrolyzed by hepatic lipase, leading to the generation of small and dense LDL particles and a decrease of the more antiatherogenic subspecies of HDL[13, 34]. Increased free fatty acid was generated from hydrolysis of the triglyceride in VLDL particles by lipoprotein lipase in the peripheral circulation, which stimulates the hepatic production of apoB-containing particles[34]. Therefore, elevated triglyceride, increased apoB, and low HDL-C are closely linked in a background of decreased insulin sensitivity. In our study, only serum triglyceride, HDL-C and apoB levels showed significant differences between CHD and non-CHD patients. In line with these findings, the degree of insulin resistance as evaluated by HOMA-IR and the percentage of subjects with metabolic syndrome were much higher in CHD patients compared with non-CHD patients. Our findings suggested that increased serum triglyceride and apoB concentrations and decreased HDL-C concentration together with insulin resistance contributed to the risk of CHD.

The causal role of elevated LDL-C in the development of atherosclerosis is beyond doubt[13]. In this cross-sectional study, we didn't find a significant difference of LDL-C between CHD and non-CHD patients or an independent association of LDL-C with CHD. The increased formation of small, dense cholesterol-depleted LDL particles, which is associated with an increased risk of myocardial infarction[39], cardiovascular events[40] and worsened severity of CHD[41], may be the explanation. A significant difference of nonHDL-C between CHD and non-CHD patients or an independent association of nonHDL-C with CHD was also not demonstrated in this study. However, our study supported an important role of apoB which represents the number of the entire spectrum of atherogenic lipoprotein particles in the

circulation[17]. In our study, apoB concentrations were significantly different between CHD and non-CHD patients, and higher apoB levels were associated with an increased risk of CHD. These findings may suggest that the number of atherogenic lipoprotein particles may be a better predictor of CHD than LDL-C and nonHDL-C, which was consistent with previous studies[18-22].

Although statins have a great potential to lower the risk of CHD, data about the effectiveness of various statins given at different intensity are still lacking in Chinese population. In a study from South Korea, low to moderate-intensity statin was effective in lowering LDL-C in diabetic patients, with 70.3% and 83.0% of patients reaching the goal of a LDL-C level less than 2.6 mmol/L in low and moderate-intensity statin treatment groups, respectively. In our study, statins were effective in improving all lipid parameters including total cholesterol, triglyceride, LDL-C, HDL-C, nonHDL-C, remnant cholesterol, apoA-I, and apoB as shown in Table 2. After adjusting for multiple confounding, the concentrations of triglyceride, HDL-C, remnant cholesterol, and apoB showed significant differences between CHD and non-CHD subjects in non-statin users in our study. However, these differences disappeared between CHD and non-CHD subjects in statin users, indicating the efficacy of statins in improving multiple lipid parameters besides LDL-C. The mean daily doses of statins used in our patients were relatively low, corresponding to a moderate-intensity statin treatment dose. Although the low daily doses, over 80% of the statin users reached a LDL-C goal of 2.6 mmol/L, and over 55% reached a LDL-C goal of 1.8 mmol/L, with no significant difference between CHD and non-CHD patients. Consistent with the previous study in Koreans[42], our findings suggested that low to moderate-intensity statin treatment may be

appropriate to achieve a desirable target values of LDL-C in Chinese population. Prospective intervention studies regarding the intensity of statin treatment in Chinese are needed in the future for a better prevention and treatment strategy of CVD in Chinese.

The advantages of our study include a large sample size, using coronary angiography to diagnose CHD, a complete measurement of lipid parameters, and adjustment of a series of confounding in the analysis. Some limitations should be addressed for our study. Firstly, a causal relationship between triglyceride, HDL-C, apoB and CHD cannot be established due to the cross-sectional study design. However, our study provided evidences that these lipid parameters may take part in the development of CHD in Chinese population and their effects on CHD cannot be ignored. Secondly, physical activity which has significant effect of lipids profile was not evaluated in our study. Thirdly, our study was performed in a population with suspected CHD, and a high proportion of CHD was confirmed by coronary angiography. Therefore, our conclusions cannot give extended application to the general population.

In conclusion，serum triglyceride, HDL-C and apoB levels were independently associated with CHD in a Chinese population undergoing coronary angiography with a relatively low level of LDL-C and a high prevalence of hypertriglyceridemia and low HDL-C. Insulin resistance may contribute to the observed associations of serum triglyceride, HDL-C and apoB with CHD. More genetic studies and intervention studies are needed to confirm the causal associations between these lipid parameters and CHD.

Conflicts of interest: There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Contributions: Each of us acknowledges that he or she participated sufficiently in the work

to take public responsibility for its content.. All authors of this paper have read and approved the final version submitted.

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Figure Legends

Figure 1 Prevalence of different types of dyslipidemia in non-statin users

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglyceride.

Figure 2 Statin species, statin doses and low-density lipoprotein cholesterol lowering effect in statin users

A Percentage of different statin use in statin users

B Mean daily doses of different statins in statin users

C Mean low-density lipoprotein cholesterol levels in statin users

D Percentage of reaching a low-density lipoprotein cholesterol (LDL-C) goal of <2.6mmol/L or <1.8mmol/L in statin users

CHD: coronary heart disease.

Figure 3 Insulin resistance and metabolic syndrome in non-statin users

A Homeostasis model assessment of insulin resistance (HOMA-IR) index in patients with and without coronary heart disease (CHD) (patients with a known history of diabetes were excluded)

B Percentage of metabolic syndrome (MS) in patients with and without CHD

C Percentage of different number of MS components in patients with and without CHD

Figure 4 The effect of insulin resistance on lipoprotein production

In the background of insulin resistance, increased hepatic free fatty acid (FFA) uptake leads to an over-secretion of apoB-containing and triglyceride-rich VLDL particles. An increased activity of cholesteryl ester transfer protein (CETP) and hepatic lipase may accompany with

insulin resistance. CETP facilitates the exchange of cholesteryl ester in LDL and HDL particles for triglyceride in VLDL particles. During the process of exchange, LDL and HDL particles become triglyceride-rich and cholesterol-depleted. These triglyceride-rich particles which are easily hydrolyzed by hepatic lipase, leads to the over-production of small and dense LDL and less antiatherogenic HDL_3 particles. The change of lipoprotein production makes the atherogenic lipids profile: hypertriglyceridemia, low HDL-C, and increased number of small and dense LDL particles. Normal or slightly elevated LDL-C and increased apoB levels also accompany with the change of lipoprotein production.

Abbreviations: VLDL: very low-density lipoprotein; LDL: low-density lipoprotein; IDL: intermediate-density lipoprotein; HDL: high-density lipoprotein; sdLDL: small and dense low-density lipoprotein; TG: triglyceride; CE: cholesteryl ester.

Table 1 Characteristics of the study population by coronary heart disease and non-coronary heart disease

Variables	CHD (n=1363)	Non-CHD (n=578)	P value
Male (%)	78.14	59.20	<0.001
Age (years)	62.18±0.26	59.05±0.40	<0.001
BMI (Kg/m^2)	24.71±0.08	24.58±0.13	0.36
WC (cm)	87.72±0.25	86.30±0.42	0.003
FPG (mmol/L)	5.59±0.04	5.16±0.04	<0.001
2-h PPG (mmol/L)	9.22±0.11	7.75±0.14	<0.001
HbA1c (%)	6.23±0.03	5.93±0.04	<0.001
Diabetes (%)	37.34	26.39	<0.001
SBP (mmHg)	130.92±0.43	128.79±0.62	0.01
DBP (mmHg)	78.53±0.26	78.78±0.39	0.60
Hypertension (%)	71.31	64.46	<0.001
Total cholesterol (mmol/L)	4.12±0.03	4.16±0.04	0.42
Triglyceride (mmol/L)	1.51 (1.10-2.10)	1.40 (1.00-2.00)	0.05
LDL-C (mmol/L)	2.23±0.02	2.26±0.03	0.55
HDL-C (mmol/L)	1.12±0.01	1.18±0.01	<0.001
nonHDL-C (mmol/L)	3.01±0.03	2.98±0.04	0.58
Remnant cholesterol (mmol/L)	0.70 (0.50-0.99)	0.61 (0.47-0.90)	0.01
apoA-I (g/L)	1.16±0.01	1.17±0.01	0.16
apoB (g/L)	0.74±0.01	0.72±0.01	0.11
Statin use (%)	27.51	18.58	<0.001
Smoking states			
Non-smokers (%)	47.32	67.01	
Ex-smokers (%)	10.36	7.12	<0.001
Current smokers (%)	42.32	25.87	
Drinking states			
Non-drinkers (%)	72.19	77.26	
Ex-drinkers (%)	3.67	3.47	<0.001
Current drinkers (%)	24.14	19.27	

Continuous data are expressed as mean±SEM or median (interquartile range).
BMI: body mass index; FPG: fasting plasma glucose; 2-h PPG: 2-hour postprandial plasma glucose; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; nonHDL-C: non-high-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B.

Table 2 Characteristics of the study population by statin use and no statin use

Variables	Statin use (n=482)	No statin use (n=1459)	P value
Male (%)	74.27	71.90	0.31
Age (years)	62.65±0.45	60.80±0.25	<0.001
BMI (Kg/m^2)	24.75±0.14	24.64±0.08	0.48
WC (cm)	87.44±0.42	87.26±0.25	0.72
FPG (mmol/L)	5.54±0.06	5.44±0.04	0.17
2-h PPG (mmol/L)	8.98±0.18	8.70±0.10	0.17
HbA1c (%)	6.15±0.05	6.14±0.03	0.87
Diabetes (%)	34.65	33.86	0.75
SBP (mmHg)	128.75±0.66	130.79±0.42	0.01
DBP (mmHg)	77.59±0.41	78.94±0.25	0.01
Hypertension (%)	71.16	67.44	0.13
Total cholesterol (mmol/L)	3.79±0.04	4.25±0.02	<0.001
Triglyceride (mmol/L)	1.32 (0.97-1.97)	1.52 (1.10-2.10)	0.001
LDL-C (mmol/L)	1.88±0.04	2.36±0.02	<0.001
HDL-C (mmol/L)	1.19±0.02	1.12±0.01	<0.001
nonHDL-C (mmol/L)	2.60±0.04	3.13±0.02	<0.001
Remnant cholesterol (mmol/L)	0.60 (0.44-0.89)	0.70 (0.50-1.00)	<0.001
apoA-I (g/L)	1.23±0.01	1.14±0.01	<0.001
apoB (g/L)	0.67±0.01	0.76±0.01	<0.001
Smoking states			
Non-smokers (%)	51.35	53.77	
Ex-smokers (%)	10.19	9.12	0.60
Current smokers (%)	38.46	37.11	
Drinking states			
Non-drinkers (%)	73.86	73.68	
Ex-drinkers (%)	5.39	3.02	0.04
Current drinkers (%)	20.75	23.30	

Continuous data are expressed as mean±SEM or median (interquartile range).
BMI: body mass index; FPG: fasting plasma glucose; 2-h PPG: 2-hour postprandial plasma glucose; HbA1c: glycosylated hemoglobin; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; nonHDL-C: non-high-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B.

Table 3 Association of lipid parameters with coronary heart disease in 1459 patients without statin use

Variables	Quartiles				P for trend*
	1	2	3	4	
Total cholesterol (mmol/L)	3.16±0.02	3.90±0.01	4.49±0.01	5.51±0.03	
OR (95%CI)*	1	1.19 (0.85-1.67)	0.99 (0.72-1.38)	1.38 (0.99-1.94)	0.15
Triglyceride (mmol/L)	0.90 (0.77-1.00)	1.30 (1.20-1.40)	1.80 (1.65-1.96)	2.70 (2.40-3.20)	
OR (95%CI)*	1	1.65 (1.18-2.30)	1.43 (1.03-1.99)	1.95 (1.38-2.74)	0.001
LDL-C (mmol/L)	1.36±0.02	2.05±0.01	2.59±0.01	3.46±0.03	
OR (95%CI)*	1	0.78 (0.56-1.08)	0.79 (0.57-1.12)	1.09 (0.78-1.54)	0.55
HDL-C (mmol/L)	0.81±0.004	1.03±0.003	1.22±0.003	1.56±0.013	
OR (95%CI)*	1	0.72 (0.52-0.99)	0.67 (0.47-0.95)	0.58 (0.40-0.85)	0.005
nonHDL-C (mmol/L)	2.01±0.02	2.81±0.01	3.49±0.01	4.54±0.04	
OR (95%CI)*	1	1.21 (0.88-1.68)	1.09 (0.79-1.51)	1.80 (1.23-2.64)	0.01
Remnant cholesterol (mmol/L)	0.40 (0.35-0.49)	0.60 (0.57-0.70)	0.90 (0.82-1.00)	1.37 (1.22-1.60)	
OR (95%CI)*	1	1.67 (1.22-2.30)	1.55 (1.13-2.14)	2.13 (1.44-3.14)	<0.001
apoA-I (g/L)	0.93±0.004	1.08±0.002	1.19±0.002	1.44±0.009	
OR (95%CI)*	1	1.18 (0.82-1.68)	1.07 (0.78-1.47)	1.05 (0.76-1.45)	0.79
apoB (g/L)	0.53±0.004	0.68±0.002	0.84±0.002	1.09±0.02	

OR (95%CI)*	1	1.03 (0.74-1.44)	1.34 (0.99-1.81)	1.69 (1.16-2.45)	0.003

Variables are expressed as mean±SEM or median (interquartile range).

*Adjusted for age, sex, BMI, diabetes, hypertension, smoking and alcohol-drinking.

LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; nonHDL-C: non-high-density lipoprotein cholesterol; apoA-I: apolipoprotein A-I; apoB: apolipoprotein B.

Figure 1

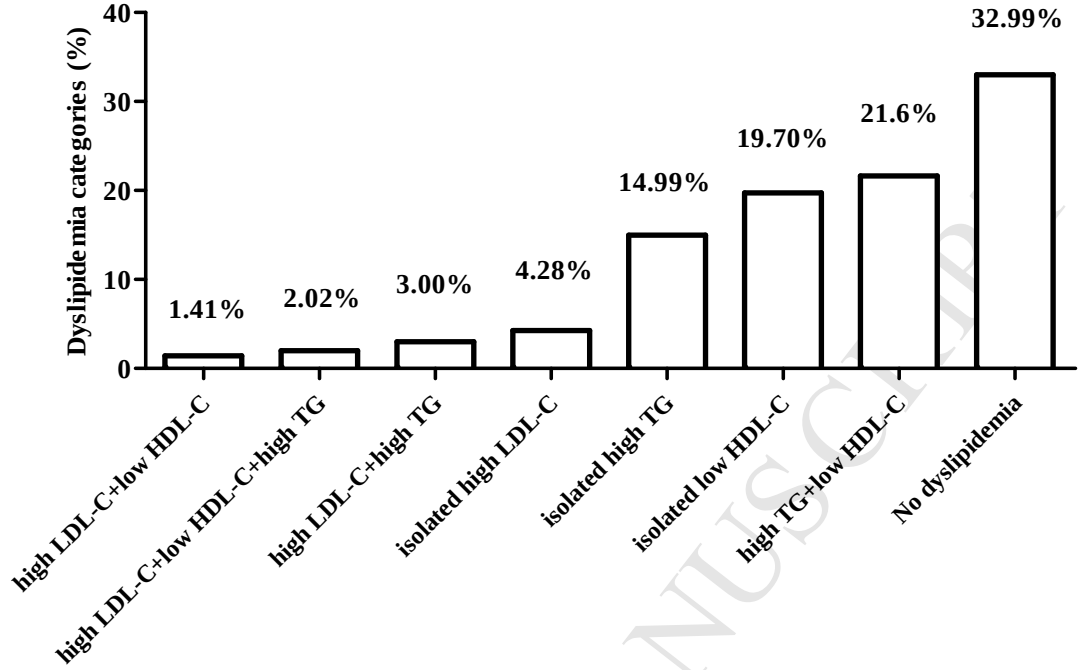


Figure 2

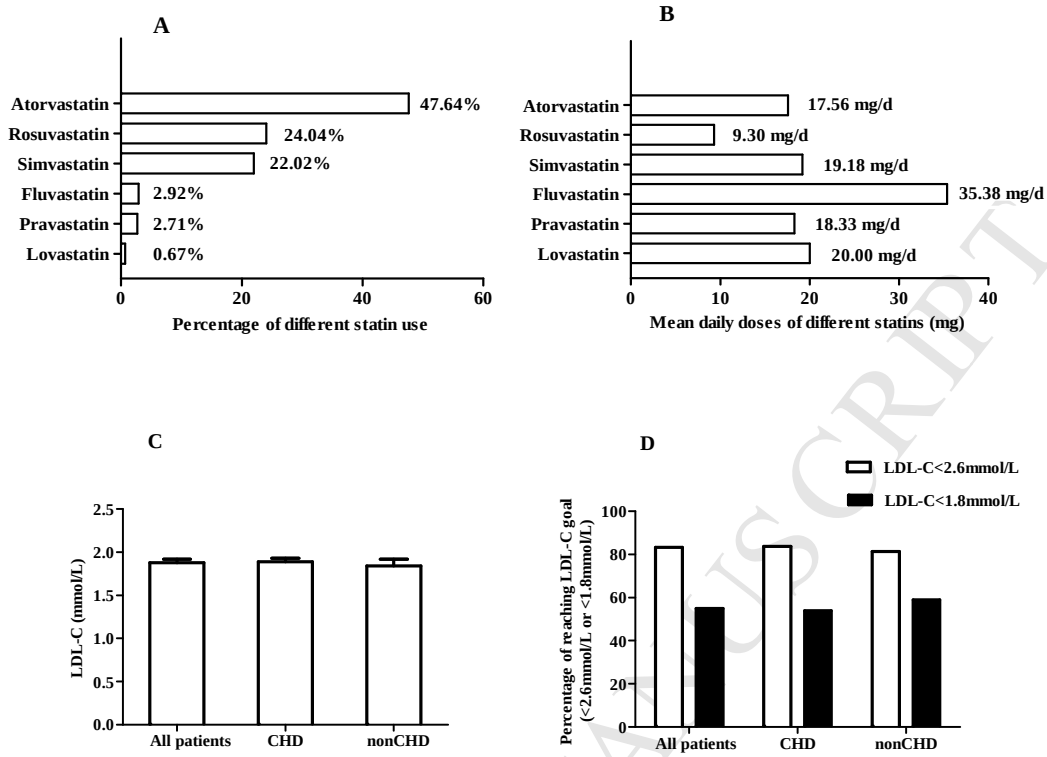
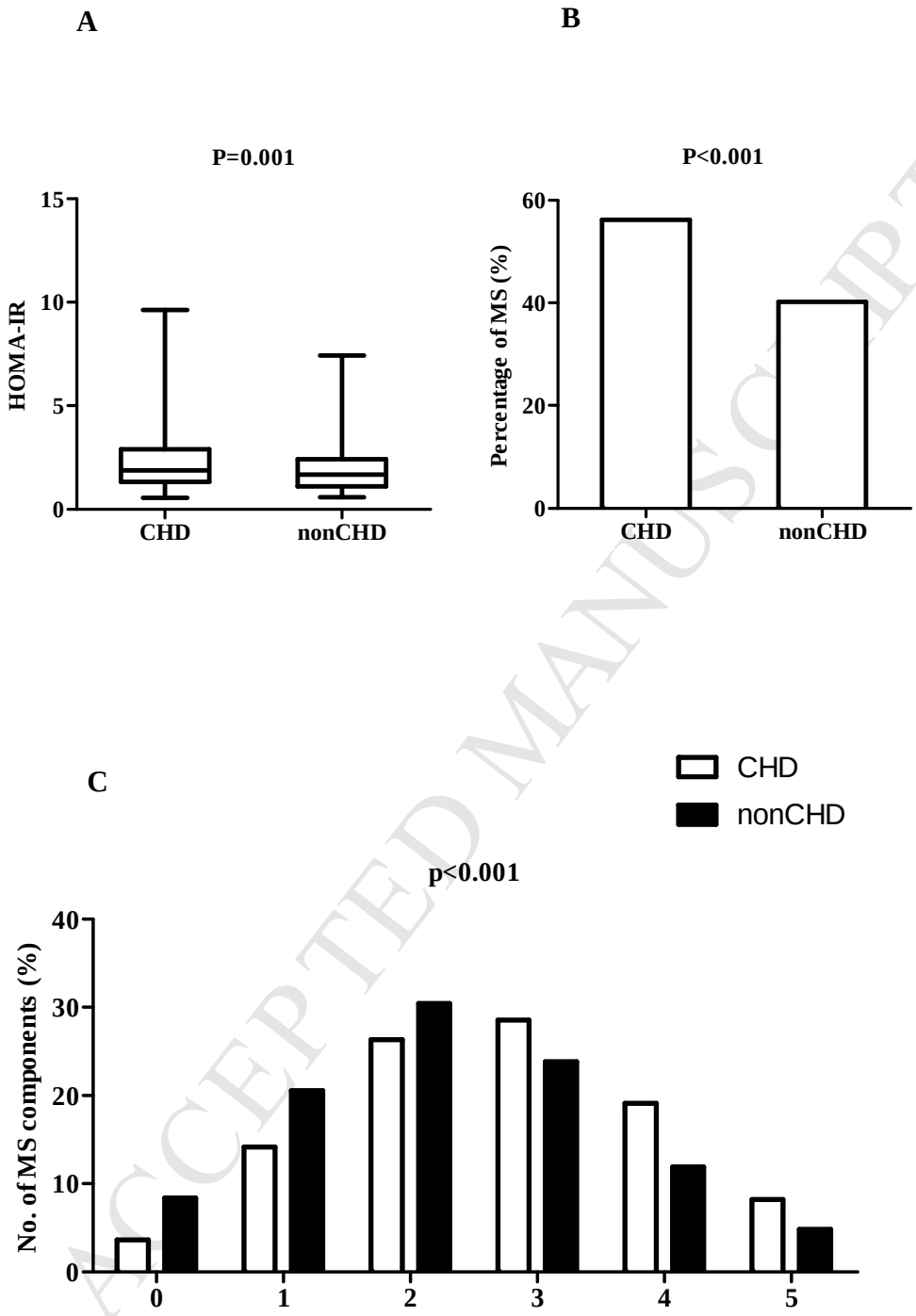
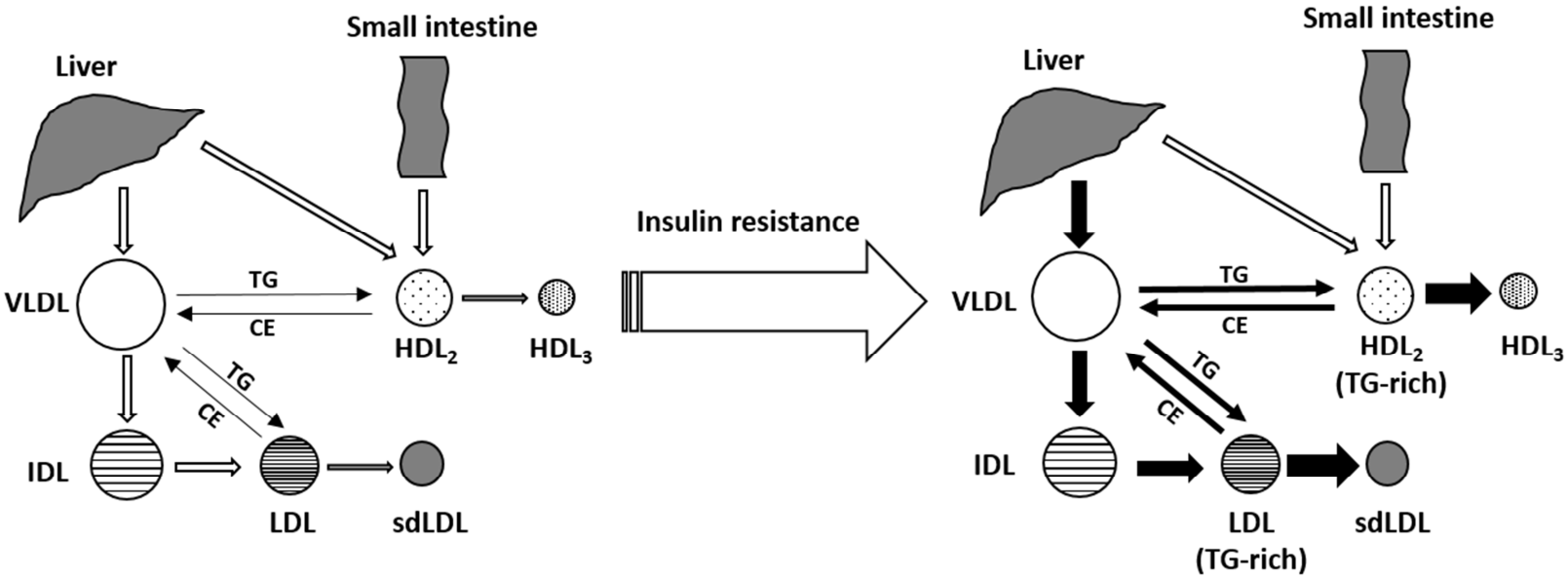


Figure 3




Liver
Small intestine
VLDL
TG
CE
HDL2
HDL3
TG
CE
IDL
LDL
sdLDL
Insulin resistance
Liver
Small intestine
VLDL
TG
CE
HDL2
(TG-rich)
HDL3
TG
CE
IDL
LDL
(TG-rich)
sdLDL

Highlights

- 1941 consecutive patients referred to coronary angiography are recruited.
- There is a high prevalence of hypertriglyceridemia and low HDL-C in the population.
- Triglyceride, HDL-C and apoB levels are different between CHD and non-CHD patients.
- Triglyceride, HDL-C and apoB levels are independently associated with CHD.