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Persistent lipid abnormalities in statin-treated coronary artery disease patients with and without diabetes in China

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ABSTRACT

Background: We evaluate the prevalence of persistent lipid abnormalities and statin use in Chinese coronary artery disease patients with and without diabetes.

Methods and results: In this cross-sectional observational study, 8965 outpatients from 200 clinical departments of 122 hospitals in 27 provinces nationwide of China who had coronary artery disease and were taking a statin were consecutively enrolled and divided into two groups based on diabetes status. The European Society of Cardiology/European Arthrosclerosis Society Guidelines for the management of dyslipidemias and the Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults were used to compare the control rates of low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, and triglycerides (TG). Among the 8965 participants, 33.3% had been diagnosed with diabetes mellitus. According to the ESC Guidelines, the percentage of patients with not at goal LDL cholesterol did not differ significantly between patients with diabetes and those without diabetes (71.9% vs. 72.7%, $P = 0.46$). The percentages of patients with not-at-goal levels of HDL and TG were 42.9% vs. 34.4% ($P < 0.001$) and 39.1% vs. 34.3% ($P < 0.001$) among patients with diabetes and those without, respectively. Only approximately 10% of patients in both groups had optimal LDL-C, HDL-C, and TG levels. Compared with patients without diabetes, patients with diabetes were more likely to have mixed dyslipidemia. Atorvastatin (47.0%) and simvastatin (34.4%) were the two most frequently used statins, and the average statin dosage was 29.09 mg/day (simvastatin equivalent). Less than 1% of patients were treated with another lipid-lowering drug in combination with a statin.

Conclusions: Although international guidelines highly recommend intensive lipid modulation in patients with coronary artery disease, persistent dyslipidemia is still prevalent among these patients in China, even with statin treatment.

1. Introduction

Coronary artery disease (CAD) involves atherosclerosis of arteries via the slow progression of luminal narrowing. Atherosclerotic plaques are characterized by the storage of apolipoprotein B-containing lipoproteins in the space under the endothelium [1]. Lipid accumulation activates dendritic cells, macrophages, smooth muscle cells, and T cells, leading to maladaptive inflammatory responses [2]. Because dyslipidemia increases the probability of atherosclerosis, it is a risk factor for CAD.

A prospective meta-analysis involving 14 randomized trials of statins including 90,056 individuals showed that with every 1.0 mmol/L reduction in low-density lipoprotein cholesterol (LDL-C), the 5-year incidence rate of major coronary events, coronary revascularization, and stroke decreases by 20%, independent of the initial lipid level [3]. Many other studies have also concluded that statins are the optimal medication for treating dyslipidemia, especially that related to LDL-C and total cholesterol (TC) [4–7].

Although international guidelines recommend statin therapy to decrease the risk of cardiovascular disease (CVD), the rate of LDL-C control is only 40–50% in countries other than China that are involved in the Dyslipidemia International Study (DYSIS), according to the European Society of Cardiology (ESC)/European Arthrosclerosis Society (EAS) Guidelines for the management of dyslipidemias. Compared to that in all patients, the rate of control in patients with a very high risk of CVD is approximately 10% lower [8–10]. In China, CAD is the second leading cause of premature death. The data from the Global Burden of Diseases, Injuries, and Risk Factors Study 2010 (GBD 2010) for 1990 and 2010 in China showed that the age-standardized mortality for coronary heart

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Table 1
Patient characteristics.

	All patients N = 8965	CAD with DM N = 2982	CAD without DM N = 5983	P[a]
Age, years, mean ± SD	70.33 ± 10.23	71.02 ± 10.19	70.00 ± 10.24	<0.001
Female, % (n/N)	42.1 (3773/8965)	45.1 (145/2982)	40.6 (2428/5983)	<0.001
First-degree family history of premature CVD, % (n/N)	11.6 (1037/8960)	11.7 (350/2979)	11.5 (687/5981)	0.71
Current smoker, % (n/N)	11.9 (1070/8965)	12.3 (368/2982)	11.7 (702/5983)	0.40
Sedentary lifestyle, % (n/N)	21.6 (1940/8964)	25.3 (759/2981)	19.7 (1181/5983)	<0.001
BMI, kg/m^2, mean ± SD (n)	24.72 ± 3.33 (8960)	25.17 ± 3.32 (2980)	24.49 ± 3.30 (5980)	<0.001
BMI <25 kg/m^2 (normal weight), % (n/N)	55.7 (4991/8960)	50.0 (1491/2980)	58.5 (3500/5980)	<0.001
BMI 25–30 kg/m^2 (overweight), % (n/N)	38.7 (3466/8960)	42.7 (1273/2980)	36.7 (2193/5980)	
BMI >30 kg/m^2 (obese), % (n/N)	5.6 (503/8960)	7.2 (216/2980)	4.8 (287/5980)	
Waist circumference ≥90 cm (M), ≥80 cm (W), % (n/N)	58.7 (5222/8902)	65.2 (1935/2968)	55.4 (3287/5934)	<0.001
PAD, % (n/N)	1.8 (157/8965)	2.3 (70/2982)	1.5 (87/5983)	0.002
Cerebrovascular disease, % (n/N)	15.8 (1420/8965)	20.6 (613/2982)	13.5 (807/5983)	<0.001
Heart failure, % (n/N)	8.5 (766/8965)	11.8 (352/2982)	6.9 (414/5983)	<0.001
Hypertension, % (n/N)	73.8 (6613/88965)	83.3 (2484/2982)	69.0 (4129/5983)	<0.001
SBP, mm Hg, mean ± SD	130.71 ± 16.04	132.78 ± 16.87	129.68 ± 15.50	<0.001
DBP, mm Hg, mean ± SD	77.29 ± 9.81	77.24 ± 10.31	77.32 ± 9.55	0.73
Blood pressure <140/90 mm Hg, % (n/N)	66.5 (5962/8965)	61.3 (1827/2982)	69.1 (4135/5983)	<0.001
Blood pressure <130/80 mm Hg, % (n/N)	28.0 (2506/8965)	257 (765/2982)	29.1 (1741/5983)	0.001
Fasting plasma glucose, mmol/L, mean ± SD	6.17 ± 2.10 (4906)	7.52 ± 2.82 (1721)	5.46 ± 1.00 (3185)	<0.001
HbA1c, median (IQR) (n)	6.6 (5.9–7.6) (1687)	7.0 (6.5–8.1) (1257)	5.8 (5.4–6.0) (430)	<0.001[b]

CAD, coronary artery disease; DM, diabetes mellitus; CVD, cardiovascular disease; M, men; W, women; PAD, peripheral arterial disease; SBP, systolic blood pressure; and DBP, diastolic blood pressure.
[a] P < 0.05, based on independent samples t test or separate variance estimation t-test comparing results for patients with and without DM.
[b] P < 0.05 based on the Mann–Whitney U test.

disease increased from 55.7 per 100,000 people in 1990 to 77.1 in 2010 [11]. Diabetes mellitus (DM) is a CAD equivalent disease [4]; that is, for patients with DM and no history of myocardial infarction, the risk of CVD is as high as that in patients with a history of myocardial infarction and without DM [12]. However, there is a paucity of data needed to estimate average lipid levels in CAD patients in China and to assess the differences between patients with and without DM. The objective of the present study was to analyze the prevalence of dyslipidemia and lipid-lowering drug use in Chinese patients with CAD. Moreover, we also present the current situation of lipid lowering therapy and the importance of intensive lipid lowering therapy to achieve optimal lipid levels.

2. Methods

2.1. Study population

This study was a subgroup analysis of the DYSIS-China. 8965 outpatients from 200 clinical departments of 122 hospitals in 27 provinces nationwide of China who had coronary artery disease and were taking statin were consecutively enrolled and divided into two groups based on diabetes status. All patients who were 45 years or older had been treated with statin for at least 3 months, and were diagnosed with CAD by invasive or non-invasive tests, such as stress electrocardiography (ECG), stress echocardiography, nuclear imaging, computed tomography angiography (CTA), and coronary angiography (CAG), or diagnosed after myocardial infarction, percutaneous coronary intervention (PCI), or coronary artery bypass grafting (CABG). Patients actively participating in another clinical study were excluded.

2.2. Data collection

Lipid parameters from the last lipid test 6–12 months previously for TC, LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were recorded. The ESC/EAS Guidelines for the management of dyslipidemias [6] and the Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults [4] were used for risk stratification of patients and to stipulate the LDL-C goal, low HDL-C levels, and elevated TG levels.

We recorded patients' age and gender as well as clinical variables related to CAD (Table 1). Cut-off values for waist circumference were at least 90 cm for men and 80 cm for women, and DM was diagnosed by serum glucose of at least 7.0 mmol/L, HbA1c no less than 6.5%, current use of diabetes therapy, or previous DM diagnosis. Information regarding statin use, including the type and dosage, was collected, and statin dose was normalized to six different simvastatin doses [13,14]. The use of other lipid-modifying drugs in combination with a statin also was recorded.

2.3. Lipid targets

Based on the ESC/EAS Guidelines for the management of dyslipidemias, for CAD patients, the LDL-C target is <1.8 mmol/L. According to the Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults, the patients were divided into two groups based on dyslipidemia risk stratification: high-risk and very high-risk groups. The lipid targets differ between the two groups [4].

2.4. Statistical analysis

Continuous variables are given as means with standard deviations or medians with 25th and 75th percentiles (interquartile range). Categorical variables are shown as percentages and absolute numbers. Independent samples t tests, separate variance estimation t tests, or Mann–Whitney U tests were used for comparisons of continuous variables. Chi-square tests were used to compare categorical values. Independent factors associated with dyslipidemia were analyzed by multiple logistic regression analysis. P < 0.05 was considered statistically significant. Statistical Product and Service Solutions (version 19) software was used for data analysis.

3. Results

The demographic and metabolic data for enrolled CAD patients are presented in Table 1. The patient characteristic data were based on 8965 patients, with the exceptions of fasting blood glucose and HbA1c levels, which were measured in 4906 and 1687 subjects, respectively. The percentages of patients with and without DM were 33.3% and 66.7%, respectively. Compared to patients without DM, the patients

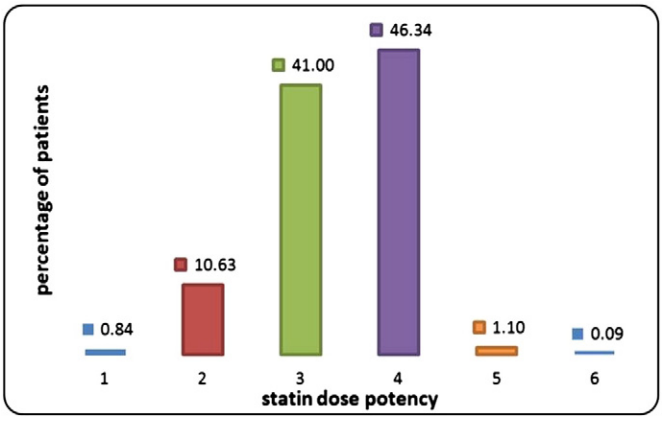

Fig. 1. Statin dose potency. The potency categories 1, 2, 3, 4, 5, and 6 are equal to simvastatin doses of 5, 10, 20, 40, 80, and 160 mg/day, respectively.

Table 2
Use of statins and combination therapy.

	With DM N = 2982	Without DM N = 5983	P
Statin dose, mg/day, simvastatin equivalent unit, mean ± SD	28.64 ± 13.53	29.32 ± 12.78	0.02[a]
Patients using nicotinic acid in addition to statin, % (n/N)	0.03 (1/2981)	0.05 (3/5983)	1.00[b]
Patients using ezetimibe in addition to statin, % (n/N)	0.2 (5/2982)	0.3 (16/5983)	0.36[b]
Patients using fibrate in addition to statin, % (n/N)	0.5 (16/2982)	0.4 (23/5983)	0.30[b]

[a] P < 0.05 based on the independent sample t test.
[b] P < 0.05 based on chi-square test or chi-square test with correction for continuity.

with DM were older (71.02 vs. 70.00 years) and more likely to be female (45.1% vs. 40.6%), have a sedentary lifestyle (25.3% vs. 19.7%), a higher body mass index (BMI; 25.17 vs. 24.49 kg/m^2), a waist circumference greater than the recommended value (65.2% vs. 55.4%), a higher systolic blood pressure (132.78 vs. 129.68 mm Hg), hypertension (83.3% vs. 69.0%), peripheral artery disease (PAD; 2.3% vs. 1.5%), cerebrovascular disease (20.6 vs. 13.5%), and a history of heart failure (11.8% vs. 6.9%). Although differences in some variables between the two groups were small, they were statistically significant (P < 0.05). However, differences in a first degree family history of premature CVD (11.7% vs. 11.5%), current smoking (12.3% vs. 11.7%), and diastolic blood pressure (77.24 vs. 77.32 mm Hg) were not statistically significant. Compared to patients without DM, those with DM had lower rates of blood pressure control (61.3% vs. 69.19% for blood pressure <140/90 mm Hg and 25.7% vs. 29.1% for <130/80 mm Hg). Because grouping was based on the presence of DM, differences in fasting plasma glucose and HbA1c were obviously significant between the groups. The 2013 ESC Guidelines on diabetes identified goals of less than 7.0% for HbA1c and less than 7.2 mmol/L for fasting plasma glucose [15]. The average glucose level in patients with DM was higher than the target value, and only about half of the patients met the target level for HbA1c. The percentages of obese patients as well as patients with a waist circumference exceeding the recommended targets in the two groups did not differ significantly. However, abdominal obesity was more common among DM patients.

3.1. Use of statins and other lipid-modifying therapies

Atorvastatin (47.0%) and simvastatin (34.4%) were the two most frequently prescribed statins, and statin dose potency 3 (41.0%) and potency 4 (46.3%), which are equivalent to 20 and 40 mg/day simvastatin, respectively, were the two most commonly used potencies (Fig. 1). Patients with DM received a larger statin dose than those without DM (29.32 vs. 28.64 mg/day simvastatin equivalent). Less than 1% of patients received a drug combination for lipid reduction. The drug most commonly used in combination with a statin was fibrate, but this regimen was used in only 0.5% of patients with DM and 0.4% of patients without DM. The percentages of patients taking combinations of statin and niacin or ezetimibe were very low and not significantly different in the two groups (Table 2).

3.2. Lipid measurements

According to the China Guidelines, in patients with and without DM, the levels of TC (4.25 vs. 4.23 mmol/L) and LDL-C (2.42 vs. 2.39 mmol/L) did not differ significantly. However, patients with DM had significantly higher rates of not-at-goal TC (83.3% vs. 48.1%, P < 0.001) and LDL-C (59.5% vs. 35.6%, P < 0.001) compared to those without DM. In addition, comparing patients with DM to those without, patients with DM had a lower HDL-C level (1.19 vs. 1.25 mmol/L), higher TG level (1.46 vs. 1.39 mmol/L), higher percentage of below-target HDL-C (37.4% vs. 29.7%, P < 0.001), higher percentage of elevated TG (39.1% vs. 34.3%, P < 0.001), and higher percentage of patients with not-at-goal three indicators for LDL-C, HDL-C and TG simultaneously (16.9% vs. 31.9%, P < 0.001; Table 3).

According to the ESC Guidelines, patients with DM group, compared to those without DM, both had a lower percentage of not-at-goal LDL-C (71.9% vs. 72.7%, P = 0.46), a higher percentage of below-target HDL-C (42.9% vs. 34.4%, P < 0.001) and higher percentage of elevated TG (39.1% vs. 34.3%, P < 0.001). Approximately 10% of patients with DM had an optimal combined score for LDL-C, HDL-C, and TG (Table 4), compared with 13% among patients without DM (P = 0.003). It was about 29% patients with not-at-goal LDL-C. Surprisingly, patients with DM had a lower rate of not-at-goal LDL-C levels than patients without DM.

3.3. Distributions of lipid abnormalities

The distributions of lipid abnormalities in the total study population, the DM group, and the non-DM group are shown in Fig. 2. An LDL-C level not at goal without other abnormalities (31.9%) was the most common profile in both the total population and both groups. Approximately 45% of the total patient population had mixed dyslipidemia. The DM group had a higher proportion of mixed dyslipidemia than the non-

Table 3
Lipid measurements based on the China Guideline.

	With DM N = 2982	Without DM N = 5983	P[a]
TC, mmol/L, mean ± SD	4.25 ± 1.24	4.23 ± 1.11	0.53
LDL-C, mmol/L, mean ± SD	2.42 ± 0.98	2.39 ± 0.91	0.15
HDL-C, mmol/L, mean ± SD	1.19 ± 0.35	1.25 ± 0.35	<0.001
TG, mmol/L, median (IQR)	1.46 (1.04–2.11)	1.39 (1.00–1.93)	<0.001
TC not at goal, % (n/N)[b]	83.3 (2458/2982)	48.1 (2879/5983)	<0.001
LDL-C not at goal, % (n/N)[c]	59.5 (1775/2982)	35.6 (2128/5983)	<0.001
Low HDL-C, % (n/N)[d]	37.4 (1115/2982)	29.7 (1779/5983)	<0.001
Elevated TG, % (n/N)[e]	39.1 (1167/2982)	34.3 (2055/5983)	<0.001
'Optimal' LDL-C, HDL-C and TG, % (n/N)	16.9 (504/2982)	31.9 (1908/5983)	<0.001

[a] Comparisons of TC, LDL-C, and HDL-C data were based on separate variance estimation t test. The TG was based on Mann–Whitney U test. Comparisons of the others were based on chi-square test.
[b] No less than 3.11 mmol/L or 4.14 mmol/L according risk stratification. For those patients with CAD and diabetes, the target value is 3.11 mmol/L. For those patients with CAD without diabetes, the target is 4.14 mmol/L [4]. Goals were defined based on risk stratification.
[c] No less than 2.07 mmol/L or 2.59 mmol/L. The target values were based on the patients with CAD with or without diabetes [4]. Goals were defined based on risk stratification.
[d] <1.04 mmol/L [4].
[e] >1.7 mmol/L [4].

Table 4
Lipid measurements based on the ESC Guidelines.

	With DM N = 2982	Without DM N = 5983	P[a]
LDL-C not at goal, % (n/N)[b]	71.9 (2145/2982)	72.7 (4348/5983)	0.46
Low HDL-C, % (n/N)[c]	42.9 (1280/2982)	34.4 (2059/5983)	<0.001
Elevated TG, % (n/N)[d]	39.1 (1167/2982)	34.3 (2055/5983)	<0.001
'Optimal' LDL-C, HDL-C, and TG, % (n/N)	10.8 (322/2982)	13.0 (778/5983)	0.003

[a] P < 0.05 based on chi-square test.
[b] ≥1.8 mmol/L [6].
[c] <1.00 mmol/L for men and <1.20 mmol/L for women [6].
[d] >1.7 mmol/L [6].

DM group (49.4% vs. 42.9%), regardless of the profiles of lipid abnormalities. The most common mixed dyslipidemia type was not-at-goal LDL-C combined with elevated TG in all groups (total population: 16.1%, DM group: 16.2%, and non-DM group: 16.1%).

3.4. Lipid abnormalities with use of statins with different potencies

With the use of statins of differing potency, the percentage of patients who achieved lipid level goals differed. According to the data presented in Table 5, the moderate, high, and low potency groups were associated with increasing TC levels in that order (4.20, 4.32, and 4.52 mmol/L, respectively) as well as increasing LDL-C levels (2.38, 2.57, and 2.58 mmol/L, respectively). For increasing HDL-C levels, the corresponding order was high, moderate, and low potencies (1.17, 1.22, and 1.31 mmol/L, respectively). Statins of moderate potency were associated with the lowest percentages of patients with not-at-goal LDL-C (71.8%) and elevated TG (35.7%) and a higher percentage of patients with optimal combined LDL-C, HDL-C, and TG scores (12.6%), compared to the other potency groups. Although the patients using the most potent statins had used near maximum statin dosages, the results did not indicate a superior effect compared to statins of moderate potency.

3.5. Risk factors independently associated with dyslipidemia

The lipid targets were the dependent variables in the multivariate logistic regression (Table 6). Female gender, a family history of premature CVD, smoking, cerebrovascular disease, and uncontrolled blood pressure were inversely correlated to achieving LDL-C goals. However, hypertension was a positive predictor for achievement of LDL-C goals. Female gender, a sedentary lifestyle, DM, heart failure, and large waist circumference were inversely correlated to achieving HDL-C goals. Female gender, smoking, DM, uncontrolled blood pressure, large waist circumference, and obesity were positive predictors of elevated TG levels. Finally, female gender, current smoking, DM, large waist circumference, and uncontrolled blood pressure were significant predictors of the combination of elevated LDL-C, low HDL-C, and elevated TG.

4. Discussion

This study was a part of the DYSIS-China study, which is a cross-sectional observational study of lipid levels in China, focusing on patients with CAD. The results clearly indicate that the rate of control of lipid levels remains very low, despite widespread use of statins among patients with CAD. Intensive statin therapy and/or combination statin therapy with another lipid-modifying therapy are needed to improve the present clinical situation. Other measures, for example, healthy diet, exercise, weight loss, and blood pressure control, should be taken to decrease the risk of cardiovascular death before or at the start of therapy.

Relative to patients without DM, patients with DM are known to have a less healthy lifestyle. They are more likely to have a sedentary lifestyle and larger BMI and waist circumference. Meanwhile, only about half of the patients among both groups had a normal BMI and

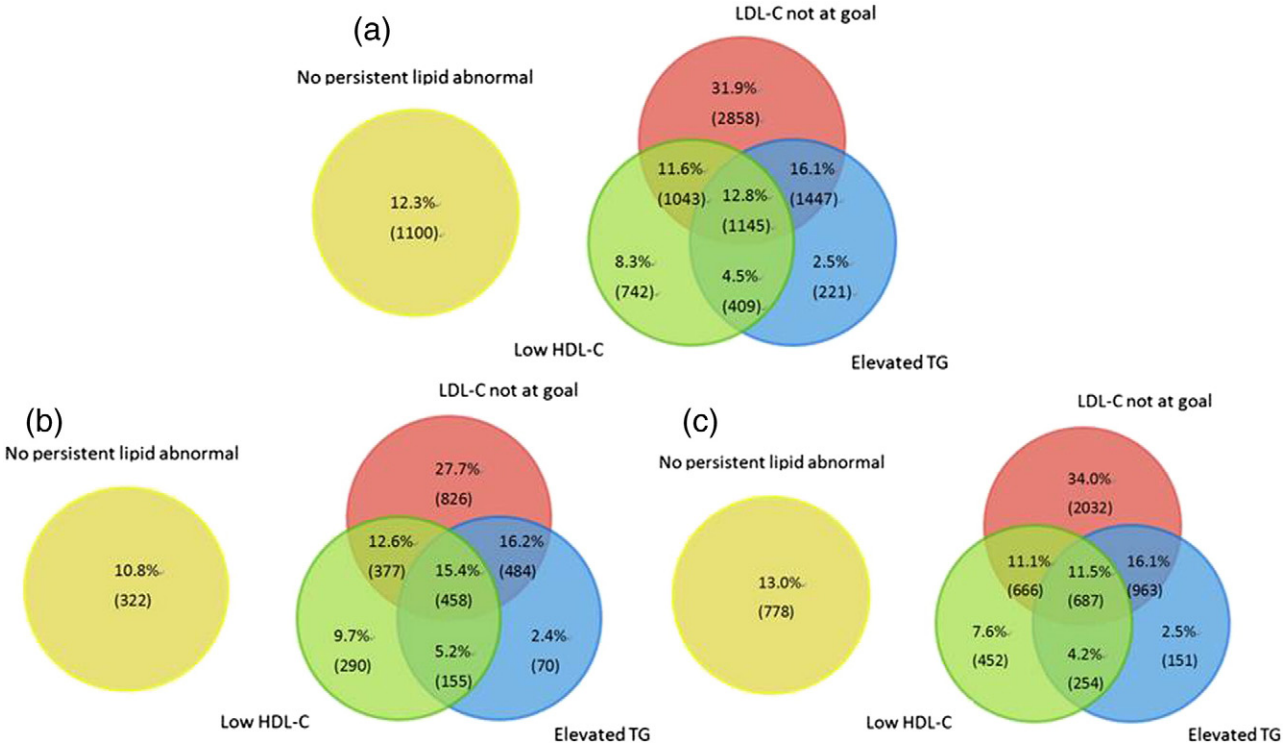

Fig. 2. The lipid data were based on 8965 patients, which included 5983 patients with DM and 2982 without DM. Venn diagrams showed the distribution of single and mixed dyslipidemias in (a) all patients in the study, (b) patients with DM, and (c) patients without DM. The lipid targets were all based on the ESC Guidelines. The yellow, red, blue, and green circles represent patients without dyslipidemia and those with not-at-goal LDL-C (no less than 1.8 mmol/L), elevated TG (more than 1.7 mmol/L), and low HDL-C (<1.0 mmol/L for men and <1.2 mmol/L for women), respectively.

Table 5
Lipid measurements based on different statin potency.

	Low potency N = 1028	Moderate potency N = 7830	High potency N = 107
TC, mmol/L, mean	4.52 ± 1.18	4.20 ± 1.14	4.32 ± 1.31
LDL-C, mmol/L, mean	2.58 ± 0.96	2.38 ± 0.92	2.57 ± 1.21
HDL-C, mmol/L, mean	1.31 ± 0.35	1.22 ± 0.35	1.17 ± 0.29
TG, mmol/L, median (IQR)	1.42 (1.01–2.05)	1.40 (1.01–1.99)	1.48 (1.06–2.05)
LDL-C not at goal, % (n/N)	77.1 (793/1028)	71.8 (5621/7830)	73.8 (79/107)
Low HDL-C, % (n/N)	28.0 (288/1028)	38.4 (3007/7830)	41.1 (44/107)
Elevated TG, % (n/N)	37.0 (380/1028)	35.7 (2799/7830)	40.2 (43/107)
'Optimal' LDL-C, HDL-C, and TG, % (n/N)	9.9 (102/1028)	12.6 (987/7830)	10.3 (11/107)

Three potencies represent different doses. Low potency includes potency categories 1 and 2. High potency includes potency categories 5 and 6. Moderate potency includes categories 3 and 4. The target lipid levels were all based on the ESC Guidelines.

waist circumference regardless of DM status. The patients with DM also had more difficulty controlling their blood pressure. Some clinical variables, such as smoking, high waist circumference, and high blood pressure, which are negative predictors for achieving the LDL-C goal, should be changed to regulate lipid levels. There is evidence that a healthy diet, exercise, and blood pressure control are beneficial to decrease the risk of CVD and improve cardiac function [16–19]. BMI and the mortality of CAD have a U-shaped relationship, and patients having a BMI greater than 25 kg/m^2 have an increased risk of cardiovascular death [20]. These results demonstrate the importance of lifestyles change and the prevention and therapy of complication for patients with CAD, especially patients with both CAD and DM.

Of the 8965 patients enrolled in this study, 88.5% were taking a statin of moderate or high potency. Despite stable statin therapy, about 75% of patients had an above-target LDL-C level. Similarly, elevated TC and TG as well as low HDL-C persisted in 34–43% of patients despite statin therapy. Although the difference was not significant, more CAD patients with DM achieved goal levels for LDL-C than did CAD patients without DM. The statin dosage and the ratio of combined therapies were slightly higher in patients with DM compared to those without DM, perhaps reflecting closer monitoring and improved treatment of patients after a diagnosis of DM. Through a comparative analysis, we found that patients with DM have more obviously mixed dyslipidemia. The variety of dyslipidemia types reflects the lipid metabolism characteristics in patients with DM [21]. Patients with elevated TG and low HDL-C need to use another lipid-modifying drug in combination with a statin for lipid regulation [22].

Among all patients in this study, only about 10% had optimal combined scores for LDL-C, HDL-C, and TG. Moreover, patients using a high potency statin did not show improved lipid control over those using a moderate potency statin. This could be the consequence of patients having higher lipid levels at the start of therapy, being unresponsive to statin therapy, or having an unhealthy lifestyle. In addition, abnormal lipid levels were common among patients taking a low potency statin, indicating that these patients likely need more intensive statin therapy.

Upon comparing statin usage between China and other regions of the DYSIS, such as the Middle East, Europe, and Canada, we determined that 20 mg and 40 mg simvastatin equivalent doses are commonly used. Nevertheless, more patients were prescribed statins of dose potency 5 and 6 in regions other than China. The difference in the percentages of patients treated with other lipid-modifying therapies with or without a statin in China and those in other countries is generally about 10% [10,23]. The low control rates for lipid levels and suboptimal use of statins indicate the importance of higher statin doses and/or statins in combination with other lipid-modifying drugs.

In previous guidelines, lipid targets were recommended according to patients' risk stratification [4,6]. However, the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults made no specific recommendation for lipid targets, in terms of the prevention of coronary heart disease, but instead only focused on the level by which LDL-C was reduced in secondary prevention, suggesting "the lower, the better" [7]. However, intensive statin therapy is needed to approach lipid goals.

Patients with DM tended to achieve LDL-C target levels more often than those without DM according to the ESC Guidelines. However, based on the China Guideline, a lower percentage of patients with DM achieved LDL-C target levels compared with that in patients without DM. This discrepancy may be explained by the different target levels for CAD patients with and without DM in the China Guideline.

There are many reasons why statin dosage may be limited, including patients' adherence, the physicians' acquaintance with and

Table 6
Multivariate logistic regression for identification of independent predictors of dyslipidemia.

	LDL-C not at goal		Low HDL-C		Elevated TG		LDL-C not at goal, low HDL-C, and elevated TG	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Age ≥70 years	n.s.	n.s.	0.74 (0.67–0.81)	<0.001	0.65 (0.60–0.72)	<0.0001	0.68 (0.59–0.77)	<0.001
Female	1.93 (1.73–2.16)	<0.001	1.24 (1.12–1.37)	<0.001	1.41 (1.27–1.58)	<0.001	1.93 (1.67–2.25)	<0.001
Family history of premature CVD	1.22 (1.04–1.42)	0.013	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
Current smoker	1.26 (1.08–1.47)	0.003	n.s.	n.s.	1.16 (1.01–1.34)	0.04	1.45 (1.16–1.81)	0.001
Sedentary lifestyle	n.s.	n.s.	1.26 (1.13–1.40)	<0.001	n.s.	n.s.	n.s.	n.s.
Alcohol consumption >2 units/week	n.s.	n.s.	0.81 (0.72–0.92)	0.001	n.s.	n.s.	n.s.	n.s.
Hypertension	0.76 (0.68–0.86)	<0.001	n.s.	n.s.	n.s.	n.s.	0.82 (0.70–0.96)	0.014
DM	n.s.	n.s.	1.37 (1.25–1.50)	<0.0001	1.15 (1.05–1.27)	0.004	1.16 (1.00–1.33)	0.047
Cerebrovascular disease	1.18 (1.03–1.35)	0.02	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
HF	n.s.	n.s.	1.39 (1.19–1.63)	<0.001	n.s.	n.s.	n.s.	n.s.
PAD	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	0.64 (0.41–0.99)	0.043
BMI ≥30 kg/m^2	n.s.	n.s.	n.s.	n.s.	1.31 (1.09–1.58)	0.004	n.s.	n.s.
Waist circumference ≥90 cm (M), ≥80 cm (W)	n.s.	n.s.	1.32 (1.20–1.45)	<0.001	1.52 (1.38–1.67)	<0.001	1.44 (1.26–1.64)	<0.001
BP ≥140/90 mm Hg	1.40 (1.26–1.56)	<0.001	n.s.	n.s.	1.15 (1.05–1.27)	0.004	1.39 (1.20–1.62)	<0.001.

The variables included in the multivariate models are listed. The lipid target levels were all based on the ESC Guidelines.
n.s.: not significant (P > 0.05), OR: odds ratio, and CI: confidence interval.

implementation of published guidelines, and the quality of the doctor–patient relationship [24]. Fear of side effects and distrust of physicians influence patient adherence. The cost of statins and a lack of awareness of CAD risk factors also were shown to reduce patient adherence [25,26]. Moreover, many physicians do not maintain knowledge of current guidelines and many simply do not use the guidelines, particularly primary care physicians [27]. In addition, the side effects of statins also affect physicians' judgments in some cases.

Clinical trials comparing statin monotherapy and statin use in combination with other drugs, including niacin [28,29], fibrate [30,31], and ezetimibe [32,33], showed that combination therapy had a significant beneficial effect on the lipid level without any significant extra clinical benefit. The combination of nacin and simvastatin is associated with a higher risk of myopathy than simvastatin monotherapy [29]. A recent systemic review of 36 randomized, controlled trials involving adults at high risk for atherosclerotic CVD compared clinical outcomes between patients taking a combination of a statin and another lipid-modifying drug and those receiving intensified statin monotherapy. Patients who were at high risk but intolerant of or unresponsive to statins could consider using the combination of a bile acid sequestrant or ezetimibe with a statin. Nonetheless, the potential long-term clinical benefits and negative side effects of the combination treatment strategy need further observation [34].

Recently, the National Institute for Health and Care Excellence (NICE) in UK announced guidelines on lipid modification for the prevention of CVD. In these new guidelines, the threshold for prescribing statins to prevent CVD is lower. The guidelines also toned down the combination therapy recommendation that fibrates should not be routinely and nicotinic acid should not be used to prevent CVD among patients who are being treated for primary and secondary prevention [35]. According to the recommendations of the 2011 ESC/EAS Guidelines for the management of dyslipidemias, the statin dosage should be increased to the upper limit before considering a drug combination. The final selection of drugs and dosages should be made by considering the composite analysis of dyslipidemia in the patients, combination treatments, and drug tolerability [6]. Thus, many guidelines have been issued to guide lipid management, but more clinical trials are needed to provide the additional evidence needed to make more informed treatment decisions.

5. Study limitations

The DYSIS is a cross-sectional and observational study, in which long-term outcomes were not evaluated and risk factors were recorded on the basis of current or retrospective data. Lipid parameters were acquired from patient medical records. There was no collection of blood samples or no core laboratory evaluation was performed to ensure the accuracy of the measurements. Statin use may be associated with selection bias for different centers. Finally, data regarding patient lifestyle, hereditary predisposition to CVD, and therapy compliance were not recorded. Nonetheless, the results of this study reflect the current situation of dyslipidemia and lipid-modifying therapy in China.

6. Conclusions

The prevalence of dyslipidemia is high among patients with CAD in China, especially in those with DM. More intensive lipid management is recommended using high-dose statins or combinations of other lipid-lowering agents with statins.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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References

[1] K.J. Williams, I. Tabas, The response-to-retention hypothesis of early atherogenesis, Arterioscler. Thromb. Vasc. Biol. 15 (5) (1995) 551–561.
[2] K.J. Moore, I. Tabas, Macrophages in the pathogenesis of atherosclerosis, Cell 145 (3) (2011) 341–355.
[3] C. Baigent, A. Keech, P.M. Kearney, L. Blackwell, G. Buck, C. Pollicino, et al., Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins, Lancet 366 (9493) (2005) 1267–1278.
[4] Joint Committee for Developing Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults, Chinese guidelines on prevention and treatment of dyslipidemia in adults, Chin. J. Cardiol. (05) (2007) 390–419.
[5] P.S. Jellinger, D.A. Smith, A.E. Mehta, O. Ganda, Y. Handelsman, H.W. Rodbard, et al., American Association of Clinical Endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis, Endocr. Pract. 18 (Suppl. 1) (2012) 1–78.
[6] Z. Reiner, A.L. Catapano, G. De Backer, I. Graham, M.R. Taskinen, O. Wiklund, et al., ESC/EAS Guidelines for the management of dyslipidaemias, Rev. Esp. Cardiol. 64 (12) (2011) (1168.e1-.e60).
[7] N.J. Stone, J. Robinson, A.H. Lichtenstein, C.N. Merz, C.B. Blum, R.H. Eckel, et al., ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Circulation 2013 (2013).
[8] F.J. Raal, D.J. Blom, S. Naidoo, P. Bramlage, P. Brudi, Prevalence of dyslipidaemia in statin-treated patients in South Africa: results of the DYSlipidaemia International Study (DYSIS), Cardiovasc. J. Afr. 24 (8) (2013) 330–338.
[9] D. Devroey, R.P. Radermecker, Van der Schueren BJ, B. Torbeyns, R.J. Jaken, Prevalence of persistent lipid abnormalities in statin-treated patients: Belgian results of the Dyslipidaemia International Study (DYSIS), Int. J. Clin. Pract. 68 (2) (2014) 180–187.
[10] S.N. Al Sifri, W. Almahmeed, S. Azar, O. Okkeh, P. Bramlage, C. Junger, et al., Results of the Dyslipidemia International Study (DYSIS)-Middle East: clinical perspective on the prevalence and characteristics of lipid abnormalities in the setting of chronic statin treatment, PLoS One 9 (1) (2014) e84350.
[11] G. Yang, Y. Wang, Y. Zeng, G.F. Gao, X. Liang, M. Zhou, et al., Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010, Lancet 381 (9882) (2013) 1987–2015.
[12] S.M. Haffner, S. Lehto, T. Ronnemaa, K. Pyorala, M. Laakso, Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction, N. Engl. J. Med. 339 (4) (1998) 229–234.
[13] D.J. Maron, S. Fazio, M.F. Linton, Current perspectives on statins, Circulation 101 (2) (2000) 207–213.
[14] W.C. Roberts, The rule of 5 and the rule of 7 in lipid-lowering by statin drugs, Am. J. Cardiol. 80 (1) (1997) 106–107.
[15] L. Ryden, P.J. Grant, S.D. Anker, C. Berne, F. Cosentino, N. Danchin, et al., ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD), Eur. Heart J. 34 (39) (2013) 3035–3087.
[16] F.B. Hu, W.C. Willett, Optimal diets for prevention of coronary heart disease, JAMA 288 (20) (2002) 2569–2578.
[17] R.J. Achttien, J.B. Staal, S. van der Voort, H.M. Kemps, H. Koers, M.W. Jongert, et al., Exercise-based cardiac rehabilitation in patients with coronary heart disease: a practice guideline, Neth. Heart J. 21 (10) (2013) 429–438.
[18] H. Naci, J.P. Ioannidis, Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study, BMJ 347 (2013) f5577.
[19] R. Collins, R. Peto, S. MacMahon, P. Hebert, N.H. Fiebach, K.A. Eberlein, et al., Blood pressure, stroke, and coronary heart disease. Part 2, Short-term reductions in blood pressure: overview of randomised drug trials in their epidemiological context, Lancet 335 (8693) (1990) 827–838.
[20] Y. Chen, W.K. Copeland, R. Vedanthan, E. Grant, J.E. Lee, D. Gu, et al., Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium, BMJ 347 (2013) f5446.
[21] S.B. Hachem, A.D. Mooradian, Familial dyslipidaemias: an overview of genetics, pathophysiology and management, Drugs 66 (15) (2006) 1949–1969.
[22] J.M. Chehade, M. Gladysz, A.D. Mooradian, Dyslipidemia in type 2 diabetes: prevalence, pathophysiology, and management, Drugs 73 (4) (2013) 327–339.
[23] A.K. Gitt, H. Drexel, J. Feely, J. Ferrieres, J.R. Gonzalez-Juanatey, K.K. Thomsen, et al., Persistent lipid abnormalities in statin-treated patients and predictors of LDL-cholesterol goal achievement in clinical practice in Europe and Canada, Eur. J. Prev. Cardiol. 19 (2) (2012) 221–230.

[24] W.S. Summerskill, C. Pope, 'I saw the panic rise in her eyes, and evidence-based medicine went out of the door'. An exploratory qualitative study of the barriers to secondary prevention in the management of coronary heart disease, Fam. Pract. 19 (6) (2002) 605–610.
[25] M. Lemstra, D. Blackburn, A. Crawley, R. Fung, Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis, Can. J. Cardiol. 28 (5) (2012) 574–580.
[26] Z. Reiner, Z. Sonicki, E. Tedeschi-Reiner, Public perceptions of cardiovascular risk factors in Croatia: the PERCRO survey, Prev. Med. 51 (6) (2010) 494–496.
[27] Z. Reiner, Z. Sonicki, E. Tedeschi-Reiner, Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: the PERCRO-DOC survey, Atherosclerosis 213 (2) (2010) 598–603.
[28] A.-H. Investigators, W.E. Boden, J.L. Probstfield, T. Anderson, B.R. Chaitman, P. Desvignes-Nickens, et al., Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy, N. Engl. J. Med. 365 (24) (2011) 2255–2267.
[29] H.-T.C. Group, HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment, Eur. Heart J. 34 (17) (2013) 1279–1291.
[30] M.J. Chapman, Fibrates in 2003: therapeutic action in atherogenic dyslipidaemia and future perspectives, Atherosclerosis 171 (1) (2003) 1–13.
[31] H.N. Ginsberg, M.B. Elam, L.C. Lovato, J.R. Crouse III, L.A. Leiter, P. Linz, et al., Effects of combination lipid therapy in type 2 diabetes mellitus, N. Engl. J. Med. 362 (17) (2010) 1563–1574.
[32] D. Morrone, W.S. Weintraub, P.P. Toth, M.E. Hanson, R.S. Lowe, J. Lin, et al., Lipid-altering efficacy of ezetimibe plus statin and statin monotherapy and identification of factors associated with treatment response: a pooled analysis of over 21,000 subjects from 27 clinical trials, Atherosclerosis 223 (2) (2012) 251–261.
[33] A.E. Pesaro, C.V. Serrano Jr., J.L. Fernandes, A.B. Cavalcanti, A.H. Campos, H.S. Martins, et al., Pleiotropic effects of ezetimibe/simvastatin vs. high dose simvastatin, Int. J. Cardiol. 158 (3) (2012) 400–404.
[34] K.A. Gudzune, A.K. Monroe, R. Sharma, P.D. Ranasinghe, Y. Chelladurai, K.A. Robinson, Effectiveness of combination therapy with statin and another lipid-modifying agent compared with intensified statin monotherapy: a systematic review, Ann. Intern. Med. 160 (7) (2014) 468–476.
[35] S. Rabar, M. Harker, N. O'Flynn, A.S. Wierzbicki, Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance, BMJ 349 (2014) g4356.