Variability in Plasma Lipids between Intensive Statins Therapy and Conventional-dose Statins Combined with Ezetimibe Therapy in Patients with Coronary Atherosclerosis Disease

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Research

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Abstract

Background: Dyslipidemia is one of the risks of coronary atherosclerosis disease (CAD). Intensive-dose statins or combining with ezetimibe are widely used to improve the lipid-lowering efficacy in the clinic. Recently, lipid variability has gradually gained attention to be a more reliable predictor of cardiovascular events. We aimed to investigate the variability in plasma lipids in the above two lipid-lowering strategy.

Methods: It was a multicenter retrospective study, a total of 1275 patients with CAD from January 2009 to April 2019 were divided into 2 groups: intensive statins (atorvastatin 40 mg/d or rosuvastatin 20 mg/d) group and conventional-dose statins (atorvastatin 20 mg/d or rosuvastatin 10 mg/d) combined with ezetimibe group. All patients were followed up for at least 1-year. Multiple linear regression was used to analyze the association of two lipid-lowering regimens with plasma lipids variability; and subgroup analyses of the relevant factors were applied. All verifications are verified by standard deviation (SD), coefficient of variation (CV), and variability independent of mean (VIM) triple methods.

Results: In the overall participants, the mean age was 62.3±10.4 years old, and 72.8% was male. Multivariate linear regression indicated that intensive statins group had lower variability in total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and non-high-density lipoprotein cholesterol (non-HDL-C) in all SD, CV, and VIM triple methods than statins combined with ezetimibe group (p for all <0.05). The similar results were established in the subgroup analyses based on atorvastatin or rosuvastatin, diabetes mellites or not, hypertension or not (p for all <0.05).

Conclusions: Intensive statins therapy has lower variability in TC, LDL-C, and non-HDL-C, that is, better lipids stability than statins combined with ezetimibe therapy in patients with CAD.

Introduction

Coronary atherosclerosis disease (CAD) is the most common type of arteriosclerotic cardiovascular disease (ASCVD).[1, 2] How to improve the prevention, treatment and prognosis of CAD is becoming a focus among clinical workers worldwide.[3]

Plasma lipids, including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglyceride (TG) are important clinical diagnostic indices of CAD.[4] Non-high-density lipoprotein cholesterol (non-HDL-C) refers to the sum of cholesterol in lipoproteins other than HDL-C, which has gradually become a research hot-spot of CAD in recent years.[5] Evidence suggests that coronary plaque regression has a significant positive correlation with LDL-C and non-HDL-C reduction.[6] Statins, as a class of drugs widely used to lower circulating LDL-C levels, have been to be the cornerstone of risk management of CAD.[7, 8] Nowadays, patients treated with statin monotherapy cannot achieve guideline-recommended lipids level goals. Therefore, the intensive-dose statins or combining with ezetimibe are widely used in the clinic. The lipid-lowering efficacy of intensive statins therapy are significantly better than that of conventional-dose statins therapy, and provide a significant benefit for preventing cardiovascular events.[9] Ezetimibe has a synergetic lipid-lowering effect with statins, and studies have shown that ezetimibe plus statins was significantly more effective at reducing LDL-C concentrations than ezetimibe or statins alone.[10]

Compared to the decreased absolute values, lipids variability has gradually gained attention to be a more reliable predictor of cardiovascular events in recent years.[11, 12]. The increased lipid variability can cause instability of the vascular wall, which can then increase plaque vulnerability and lead to plaque rupture, thus increase the risk of cardiovascular events.[13] However, at present, few studies have attempted to compare the lipid variability between patients used intensive statins and conventional-dose statins combined with ezetimibe. Given the cardiovascular benefits of the above two lipid-lowering strategies, it is vital to quantify the potential long-term risks to enable physicians and patients to make the choices, and figure out which strategies has the better lipid-lowering stability.

Therefore, we designed this large sample study to explore the variability in lipids between intensive statins and conventional-dose statins combined with ezetimibe in patients with CAD between.

Methods

Study Design

This was a multicenter retrospective study designed to explore the lipid stability between intensive statins and conventional-dose statins combined with ezetimibe, and the study design flow showed in figure 1. From January 2009 to April 2019, all consecutive patients with CAD who underwent lipid-lowering therapy at Sir Run Run Shaw Hospital and its medical consortium hospitals were recruited. The clinical characteristics of baseline were collected and all enrolled patients underwent retrospective computations for lipid parameters at admission and 1-year follow up. According to different lipid-lowering strategies, patients were divided into two groups: intensive statins (atorvastatin 40 mg/d or rosuvastatin 20 mg/d) group and conventional-dose statins (atorvastatin 20 mg/d or rosuvastatin 10 mg/d) combined with ezetimibe group. The primary end point was the variability in lipid parameters after lipid-lowering therapy.

This study was performed in accordance with the principles of the Declaration of Helsinki and local law and regulations. All data were collected by a trained study coordinator with a standardized case report form. Ethical approval of Sir Run Run Shaw Hospital (NO.20201217-36) was obtained.

Study population

The study population is composed of patients with CAD and dyslipidemia. The inclusion criteria of this study were shown as follows: (1) patients with dyslipidemia [LDL-C > 100 mg/dL, TG > 200 mg/dL, non-HDL-C levels > 130 mg/dL and TC levels > 190 mg/dL][14]; (2) patients with CAD; (3) patients who underwent lipid-lowering therapy and had shown good compliance; (4) lipid values during follow-up such as TC, TG, LDL-C, HDL-C were available; (5) patients with at least 3 times plasma lipids measurement within 1 year follow-up.

Patients were excluded if they had any one of the following: (1) heart failure with left ventricular ejection fraction(LVEF)below <40% or New York Heart Association (NYHA) Grade III or IV symptoms; (2) severe kidney failures (eGFR <30mL/min), severe liver diseases (ALT >3 times upper limit of normal), malignant cancers,

hypothyroidism, severe autoimmune diseases, stroke, serious infectious diseases, major surgery or trauma in the previous 4 weeks; (3) pregnant or lactating patients.

Data collection

All baseline characteristics of the patients who met the inclusion criteria were collected from hospital information system (HIS), including demographics, laboratory examination, comorbidities, medication at discharge and follow-up records. During treatment, levels of plasma TC, TG, LDL-C, non-HDL-C were measured at baseline and follow up. All blood samples were obtained after an overnight fast and measured by experienced operators in a central laboratory. Plasma TC and TG concentrations were measured by standard enzymatic method. The Friedewald formula was used to calculate the levels of LDL-C. Plasma HDL-C concentration was measured by heparin-Ca_{2+}/Ni_{2+} precipitation, while non-HDL-C was calculated as total cholesterol minus HDL-C.[15]

Definitions

According to 2013 American College of Cardiology/American Heart Association (ACC/AHA) guideline, intensive-dose statins therapy was defined as administrations of atorvastatin at dosage exceed 40 mg or rosuvastatin exceed 20 mg per day, if not, defined as conventional-dose statins.[16]

The definition of variability in this study uses the following three methods at the same time: 1) standard deviation (SD) Method: Standard deviation is used to describe the variability of the univariate during the follow-up period. That is, the arithmetic square root of the square of the difference between the three observations and the mean. 2) coefficient of variation (CV) method: CV=(SD/mean)×100(%) (standard deviation of the observed values measured at each node during the follow-up period/average number)×100(%). 3) variability independent of mean (VIM) method: $VIM=(SD/mean^{\beta})\times100(\%)$ (standard deviation of the observed values measured at each node during the follow-up period/$mean^{\beta}$)×100(%), where β is the regression coefficient using the natural logarithm of SD divided by the natural logarithm of the mean.[17]

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation (X±SD) and analyzed by using the independent samples t-test when the distributions were normal or Mann-Whitney rank test. Categorical variables are presented as percentages and frequencies and differences were analyzed with Pearson's chi-squared analysis and/or Fisher's exact test. Through the univariate analysis, variables with p value <0.05 were screened out for the test of multiple analyses. Multivariate linear regression analysis was performed to construct the prediction model between different lipid-lowering therapy and plasma lipids variability. According to lipid-lowering medication (atorvastatin or rosuvastatin), presence or absence of diabetes, presence or absence of hypertension, patients were divided into subgroups, and the association of different lipid-lowering therapy with plasma lipids variability in each subgroup was analyzed. All data were processed with SPSS 25.0 (Chicago, Illinois, USA).

Results

Baseline characteristics of study subjects according to lipid-lowering strategies.

A total of 1275 patients were enrolled, the mean age was 62.3±10.4 years old, 72.8% was male, 39.1% (498) patients treated with intensive statins, and 60.9% (777) patients treated with conventional-dose statins plus ezetimibe. Baseline clinical characteristics and laboratory examinations indexes are summarized in Table 1.

Table 1
Baseline characteristics of study subjects according to lipid-lowering therapy.

Characteristics	Overall(n=1275)	Intensive statins(n=498)	Statins combined with ezetimibe(n=777)	*P*-value
Demographics				
Age, years	62.3±10.4	61.6±10.4	62.8±10.3	0.062
Sex, male (%)	928 (72.8)	380 (76.3)	548 (70.5)	**0.028**
BMI, kg/m^2	24.7±2.8	24.6±2.8	24.8±2.8	0.230
Current smoking (%)	349 (27.4)	167 (33.5)	182 (23.4)	**<0.001**
Laboratory examination				
HbA1c (%)	5.9 (5.5, 6.7)	6.0 (5.5, 6.8)	5.9 (5.5, 6.6)	0.835
eGFR (ml/min/1.73m2)	90.9 (78.9, 99.2)	91.2 (78.2, 100.2)	90.5 (79.6, 99.0)	0.408
CRP mean, mg/L	1.52 (0.82, 2.73)	1.74 (0.89, 3.00)	1.42 (0.78, 2.62)	**0.007**
NLR mean	3.0 (2.3, 4.0)	3.1 (2.4, 4.1)	3.0 (2.3, 3.9)	0.069
TC mean, mmol/L	3.8 (3.3, 4.3)	3.6 (3.2, 4.2)	3.9 (3.4, 4.4)	**<0.001**
TC SD	790.3(492.2, 1189.8)	657.6 (397.0, 982.6)	872.5 (586.7, 1281.2)	**<0.001**
TC CV	207.6 (135.0, 300.3)	182.9 (115.8, 249.1)	228.3 (150.0, 316.6)	**<0.001**
TC VIM	9.4 (5.0, 16.2)	7.8 (4.0, 12.3)	10.8 (5.8, 17.5)	**<0.001**
TG mean, mmol/L	1.4 (1.1, 1.8)	1.4 (1.1, 1.8)	1.4 (1.1, 1.9)	0.139
TG SD	363.6 (215.2, 564.4)	342.0 (211.0, 536.2)	369.8 (216.0, 581.9)	0.304
TG CV	263.4 (177.8, 369.7)	265.3 (181.2, 369.0)	262.8 (175.1, 370.1)	0.985
TG VIM	23.5 (12.5, 40.6)	23.8 (12.9, 40.5)	23.4 (12.2, 40.7)	0.985
LDL-C mean, mmol/L	1.9 (1.6, 2.3)	1.8 (1.5, 2.2)	1.9 (1.6, 2.3)	**<0.001**

Data were expressed as mean ± SD, or number (%). BMI=body mass index, eGFR=estimated glomerular filtration rate, CRP=C-reactive protein, NLR=neutrophil to lymphocyte ratio, TC=total cholesterol, TG=triglyceride, LDL-C=low-density lipoprotein cholesterol, non-HDL-C=non-high-density lipoprotein cholesterol, SD=standard deviation, CV=coefficient of variation, VIM=variability independent of mean, PCI=percutaneous coronary intervention, MI=myocardial infarction, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor antagonists, CCB=calcium channel blocker.

Characteristics	Overall(n=1275)	Intensive statins(n=498)	Statins combined with ezetimibe(n=777)	*P*-value
LDL-C SD	655.3 (413.6, 958.1)	540.5 (310.3, 836.0)	719.6 (495.4, 1018.8)	**<0.001**
LDL-C CV	343.8 (224.8, 470.4)	291.7 (187.9, 416.6)	375.9 (259.4, 501.9)	**<0.001**
LDL-C VIM	92.2 (59.1, 127.9)	77.6 (49.0, 112.7)	101.2 (68.6, 136.9)	**<0.001**
Non-HDL-C mean, mmol/L	2.5 (2.2, 3.0)	2.5 (2.1, 2.9)	2.6 (2.2, 3.1)	**<0.001**
Non-HDL-C SD	526.6 (327.6, 819.9)	455.5 (277.0, 685.5)	601.7 (374.4, 922.9)	**<0.001**
Non-HDL-C CV	204.7 (136.4, 297.1)	180.0 (116.90, 254.0)	220.3 (149.7, 328.7)	**<0.001**
Non-HDL-C VIM	20.7 (12.4, 33.1)	17.6 (10.2, 27.2)	22.7 (13.9, 37.6)	**<0.001**
Comorbidities				
Hypertension (%)	796 (62.43)	319 (64.1)	477 (61.4)	0.368
Diabetes mellitus (%)	309 (24.24)	139 (27.9)	170 (21.9)	**0.017**
Previous PCI (%)	60 (7.59)	27 (6.4)	33 (9.0)	0.209
Previous MI (%)	8 (1.07)	18 (4.3)	13 (3.5)	0.746
Medication at discharge				
Aspirin (%)	1240 (97.25)	485 (97.4)	755 (97.2)	0.952
ACEI (%)	340 (26.67)	179 (35.9)	161 (20.7)	**<0.001**
ARB (%)	455 (35.69)	156 (31.3)	299 (38.5)	**0.011**
Beta-blocker (%)	773 (60.63)	339 (68.1)	434 (55.9)	**<0.001**
CCB (%)	329 (25.80)	108 (21.7)	221 (28.4)	**0.009**

Data were expressed as mean ± SD, or number (%). BMI=body mass index, eGFR=estimated glomerular filtration rate, CRP=C-reactive protein, NLR=neutrophil to lymphocyte ratio, TC=total cholesterol, TG=triglyceride, LDL-C=low-density lipoprotein cholesterol, non-HDL-C=non-high-density lipoprotein cholesterol, SD=standard deviation, CV=coefficient of variation, VIM=variability independent of mean, PCI=percutaneous coronary intervention, MI=myocardial infarction, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor antagonists, CCB=calcium channel blocker.

Compared with conventional-dose statins combined with ezetimibe group, patients in intensive statins group were more males (76.3% vs. 70.5%, P=0.028), more smokers (33.5% vs. 23.4%, P <0.001), greater burden of diabetes mellitus (27.9% vs 21.9%, P= 0.017) and were more likely to be treated with beta-blocker, calcium

channel blocker (CCB), angiotensin converting enzyme inhibitor (ACEI), and angiotensin receptor antagonists (ARB) (p for all <0.05). In addition, patients in intensive statins group had lower variability in plasma TC (7.8 vs. 10.8 mmol/L, P <0.001), LDL-C (77.6 vs. 100.9 mmol/L, P <0.001), and non-HDL-C (17.6 vs. 22.7 mmol/L, P <0.001) levels by VIM method. However, there was no significant difference in the variability in plasma TG levels between two groups. The similar results were found in CV and SD method.

Multiple linear regression analysis of lipid-lowering strategies to variability in plasma lipids levels in patients with CAD.

In order to accurately evaluate the effect of lipid-lowering strategies on lipid stability, linear regression was performed to estimate the relationship between lipid-lowering strategies and variability of plasma lipids levels in patients with CAD. (Table 2)

Table 2
Coefficients of combination therapy (vs. intensive therapy) for the variability of TC, TG, and LDL, non-HDL cholesterol in linear regression analysis (95% confidence interval).

	Model 1[a]		Model 2[b]		Model 3[c]	
	β coefficient(95% CI)	P value	β coefficient(95% CI)	P value	β coefficient(95% CI)	P value
TC variability						
VIM	3.6(2.7 to 4.5)	**<0.001**	3.8(2.8 to 4.7)	**<0.001**	3.6(2.7 to 4.6)	**<0.001**
CV	49.7(37.0 to 62.4)	**<0.001**	52.0(39.0 to 65.1)	**<0.001**	50.1(37.0 to 63.3)	**<0.001**
SD*	162.9(109.5 to 216.3)	**<0.001**	179.5(125.0 to 234.0)	**<0.001**	173.0(118.1 to 227.8)	**<0.001**
TG variability						
VIM	0.7(-3.3 to 4.6)	0.742	1.7(-2.4 to 5.9)	0.411	1.0(-3.2 to 5.1)	0.655
CV	2.9(-16.8 to 22.7)	0.771	9.3(-11.2 to 29.9)	0.373	5.7(-14.9 to 26.4)	0.585
SD*	-2.1(-62.0 to 57.7)	0.944	6.2(-57.3 to 69.7)	0.849	-2.9(-66.8 to 60.9)	0.928
LDL-C variability						
VIM	23.6(18.1 to 29.0)	**<0.001**	24.2(18.6 to 30.0)	**<0.001**	23.6(17.9 to 29.3)	**<0.001**
CV	83.9(64.4 to 103.4)	**<0.001**	86.4(66.2 to 106.6)	**<0.001**	84.1(63.8 to 104.3)	**<0.001**
SD*	149.2(108.6 to 189.8)	**<0.001**	155.5(113.8 to 197.1)	**<0.001**	148.3(107.5 to 189.1)	**<0.001**
Non-HDL-C variability						
VIM	8.0(5.8 to 10.1)	**<0.001**	8.2(5.9 to 10.4)	**<0.001**	8.2(5.9 to 10.4)	**<0.001**
CV	56.7(41.4 to 72.0)	**<0.001**	58.0(42.0 to 74.0)	**<0.001**	58.3(42.2 to 74.4)	**<0.001**
SD*	139.7(97.2 to 182.2)	**<0.001**	148.6(104.3 to 192.8)	**<0.001**	147.7(103.2 to 192.3)	**<0.001**

CI=confidence interval, CV=coefficient of variation; VIM=variability independent of mean; SD=standard deviation;

Model 1[a]: Adjusted for none.

Model 2[b]: Adjusted for age, sex, body mass index, current smoking, diabetes mellitus, hypertension, mean NLR level.
Model 3[c]: Additionally adjusted for medications (aspirin, ACEI or ARB, Beta-blocker, CCB).
SD*: Additionally adjusted for the mean of corresponding plasma lipids variability.
P<0.05 was in bold.
TC, TG, LDL-C, non-HDL-C were the same as Table 1.
CHD=coronary heart disease, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, eGFR=estimated glomerular filtration rate, ALT=alanine aminotransferase.
TC, LDL-C,and non-HDL-C were the same as Figure 2.
TC, LDL-C,and non-HDL-C were the same as Figure 2.

Without any multi-variable adjusted, Model 1 showed conventional-dose statins combined with ezetimibe group had higher variability in TC levels in SD, CV and VIM methods (SD: β = 162.9, 95% confidence interval [CI] [109.5, 216.3], p<0.001; CV: β = 49.7, 95%CI [37.0, 62.4], p<0.001; VIM: β = 3.6, 95%CI [2.7, 4.5], p<0.001), higher variability in LDL-C levels (SD: β = 149.2, 95%CI [108.6, 189.8], p<0.001; CV: β = 83.9, 95%CI [64.4, 103.4], p<0.001; VIM: β = 23.6, 95%CI [18.1, 29.0], p<0.001), and higher variability in Non-HDL-C levels (SD: β = 139.7, 95%CI [97.2, 182.2], p<0.001; CV: β = 56.7, 95%CI [41.4, 72.0], p<0.001; VIM: β = 8.0, 95%CI [5.8, 10.1], p<0.001). No significant difference in TG variability were found between two groups.

After adjusted for basic characteristics (including age, sex, body mass index, current smoking, diabetes mellitus, hypertension, and mean neutrophil to lymphocyte ratio (NLR) level), the similar results were confirmed in Model 2. After further adjusted for other medications (including aspirin, ACEI or ARB, Beta-blocker, and CCB), the statins plus ezetimibe therapy had higher lipids variability than intensive statins in patients with CAD in Model 3: higher TC variability (SD: β = 173.0, 95%CI [118.1, 227.8], p<0.001; CV: β = 50.1, 95%CI [37.0, 63.3], p<0.001; VIM: β = 3.6, 95%CI [2.7, 4.6], p<0.001), LDL-C variability (SD: β = 148.3, 95%CI [107.5, 189.1], p<0.001; CV: β = 84.1, 95%CI [63.8, 104.3], p<0.001; VIM: β = 23.6, 95%CI [17.9, 29.3], p<0.001), and Non-HDL-C variability (SD: β = 147.7, 95%CI [103.2, 192.3], p<0.001; CV: β = 58.3, 95%CI [42.2, 74.4], p<0.001; VIM: β = 8.2, 95%CI [5.9, 10.4], p<0.001).

Linear regression analysis of lipid-lowering strategies to variability in plasma lipids levels in the subgroups.

To investigate whether the results were stable, subgroup analysis based on atorvastatin or rosuvastatin, diabetes mellites or not, hypertension or not (Figure 4), also suggested that intensive statins group had lower variability in TC, LDL-C and non-HDL-C levels in VIM method compare with conventional-dose statins combined with ezetimibe group (p for all<0.05). The results were like those of the primary analysis when variability of plasma lipids was represented by SD (Figure 2) or CV (Figure 3).

Discussion

The current retrospective study found that intensive statins therapy has lower variability of TC, LDL-C, and non-HDL-C than conventional-dose statins combined with ezetimibe therapy, which was further verified in the subgroup analysis.

As is well-known, plasma lipids levels play crucial roles in the development of atherosclerosis.[18] Dyslipidemia is a well-established risk factor in the pathogenesis of CAD.[19] Increased levels of LDL-C are consistently considered a major risk factor for CAD and for the development of atherosclerotic plaques in arteries.[20, 21] When LDL-C is reduced by 24 mg/dL or 38.5 mg/dL, cardiovascular risk is decreased by 22%.[22–24] A recent large-scale epidemiological investigation in China suggested that high levels of TC and LDL-C and low levels of HDL-C were the independent risk factors of early atherosclerosis, however, an increase of the levels of TC and LDL-C associated with a higher risk of late-stage atherosclerosis.[25] TG levels can be easily changed by the current diet. That is, TG levels can show considerable fluctuations, when blood samples were drawn in a fasting or fullness state.[26] Therefore, TG levels are hardly considered as the main index for assessing the effectiveness of lipid-lowering strategies. Compared with LDL-C, non-HDL-C can more directly and accurately reflect the total number of all atherogenic lipoprotein particles. In 2016, the ACC Expert Consensus Committee released new guidelines that non-HDL-C was proposed as an equivalent target to LDL-C for high risk patients.[27] Several guidelines specify treatment target levels for lipids based on the risk of CAD.[28–30]

Besides, there is a growing body of evidence showing that, in addition to target absolute levels, fluctuations in plasma lipid become more important nowadays. the Treating to New Targets (TNT) study suggested that LDL-C variability was a predictor of cardiovascular events and mortality.[11] Similar findings were recently replicated for measures of HDL-C variability in the same population.[31] Boey et al. observed that variability of LDL-C and HDL-C levels were associated with 5-year occurrence of major adverse cardiac events after surviving ST-segment elevation myocardial infarction (STEMI).[13] It has been shown that lipid lowering treatment in both animal models and humans may lead to changes of the cholesterol content of plaques,[32] which may have consequences for plaque stability.[33] It has been proved that LDL-C variability is a predictable risk factors for complex inflammatory factor (neutrophil to lymphocyte ratio, NLR).[34] Inflammatory response can increase collagen hydrolyzing activity and thrombotic potential. Therefore, high plasma lipids variability could result in instability of the vessel wall, thereby increasing the likelihood of plaque vulnerability and rupture.[13] These studies provide circumstantial evidence that increased fluctuations in lipid levels could also causally lead to a higher occurrence of adverse events.

The changes in plasma cholesterol levels result from a systematically regulated balance of its dietary and biliary absorption, de novo synthesis, and biliary secretion. Ezetimibe is a selective cholesterol inhibitor that acts on the Niemann–Pick C1-like 1 protein (NPC1L1), can inhibit the absorption of cholesterol, without affecting the absorption of triglyceride by the intestine.[35] Statins' effect on lipids profile is caused by their competitive inhibition of 3-hydroxy-3-methyl glutaryl coenzyme reductase A (HMG-CoA) reductase enzyme, which is responsible for controlling the rate-limiting step of hepatocyte cholesterol synthesis.[36] Recently, a large double-blind Randomized controlled study (RCTs) confirmed statin/ezetimibe combination had a greater effect on lowering lipids, including LDL-C and TC, compared to double-dose statin monotherapy.[37] However, minimal studies have been conducted to compare the variability in plasma lipids of medication,

the current study focused on lipids variability rather than lowering lipids effects. The result confirmed that intensive statins therapy had lower lipids variability, that was, better lipids stability than statins combined with ezetimibe therapy. The main probable reason is: Statins inhibit cholesterol synthesis, while ezetimibe inhibits cholesterol absorption in the intestinal tract. They have the synergy to achieve a stronger lipid-lowering effect. But ezetimibe might be influenced more by variability in diet, that is, higher plasma lipids variability accompanied by imbalanced intake than statin monotherapy. From the current study, intensive statins therapy had lower lipids variability, that was, better lipid stability than statins combined with ezetimibe therapy. These could possibly increase the stability of plaque, the probability of occurrence of acute adverse events might decrease as well. Moreover, patients used intensive statins therapy might be able to reduce the frequency of measuring plasma lipids due to lower variability.

Our study has some limitations that warrant discussion. First, as a retrospective study, there were inherent drawbacks. Not all clinical information and laboratory data could be collected. Second, the follow-up times of the samples in this study is not completely consistent, so patients' lipids levels might be vulnerable to different diet and environment. The risk of bias and residual confounding cannot be completely ruled out. In the future, large-scale randomized controlled trials are needed before these conclusions are to be applied elsewhere. In addition, only lipid-variability between intensive statins (atorvastatin 40 mg/d or rosuvastatin 20 mg/d) therapy and conventional-dose statins (atorvastatin 20 mg/d or rosuvastatin 10 mg/d) combined with ezetimibe therapy were compared in this study. The lipid-lowering stability of other strategies will require further exploration.

Conclusions

Intensive statins therapy has lower variability in TC, LDL-C, and non-HDL-C, that is, better lipids stability than statins combined with ezetimibe therapy in patients with CAD.

Declarations

Ethics approval and consent to participate

The study was conducted according to the Declaration of Helsinki (as revised in 2013), and was approved by the ethics committee of Sir Run Run Shaw Hospital (NO.20201217-36). No informed consent was available due to the retrospective design.

Consent for publication

All authors confirmed and approved to publication.

Availability of data and material

Definitely, the corresponding author would like to provide data for proper requests.

Competing interests

The authors declare no competing interests.

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Authors' contributions

Ya Li, Fuyu Qiu and Wenbin Zhang designed the study, and wrote the analysis plan. Jinhua Jin, Duanbin Li and Zhezhe Chen undertook analyses and all authors interpreted the results in the study. Cao Wang, Lu Liu and Tian Xu wrote the first draft of the manuscript with critical revisions from Ya Li, Fuyu Qiu and Wenbin Zhang. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors gave final approval of the version to be published.

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Figures

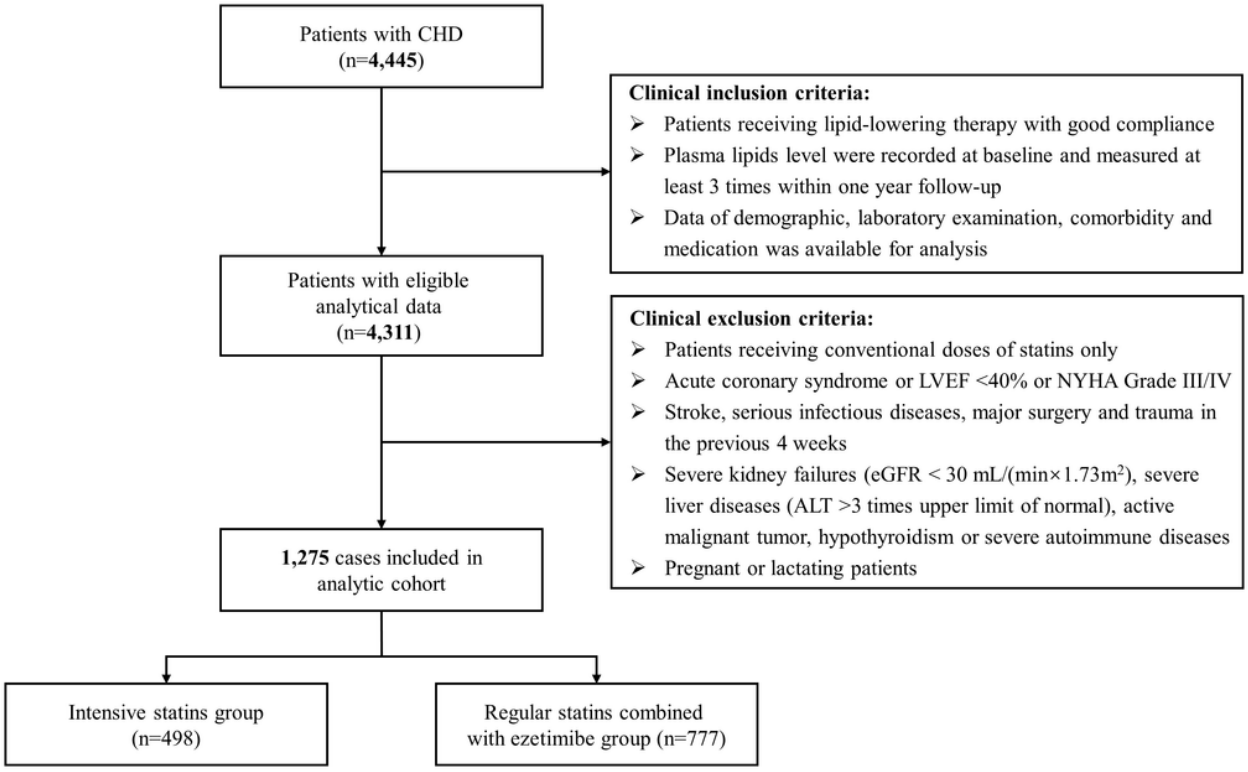

Figure 1

Flow chart for study design. CHD=coronary heart disease, LVEF=left ventricular ejection fraction, NYHA=New York Heart Association, eGFR=estimated glomerular filtration rate, ALT=alanine aminotransferase.

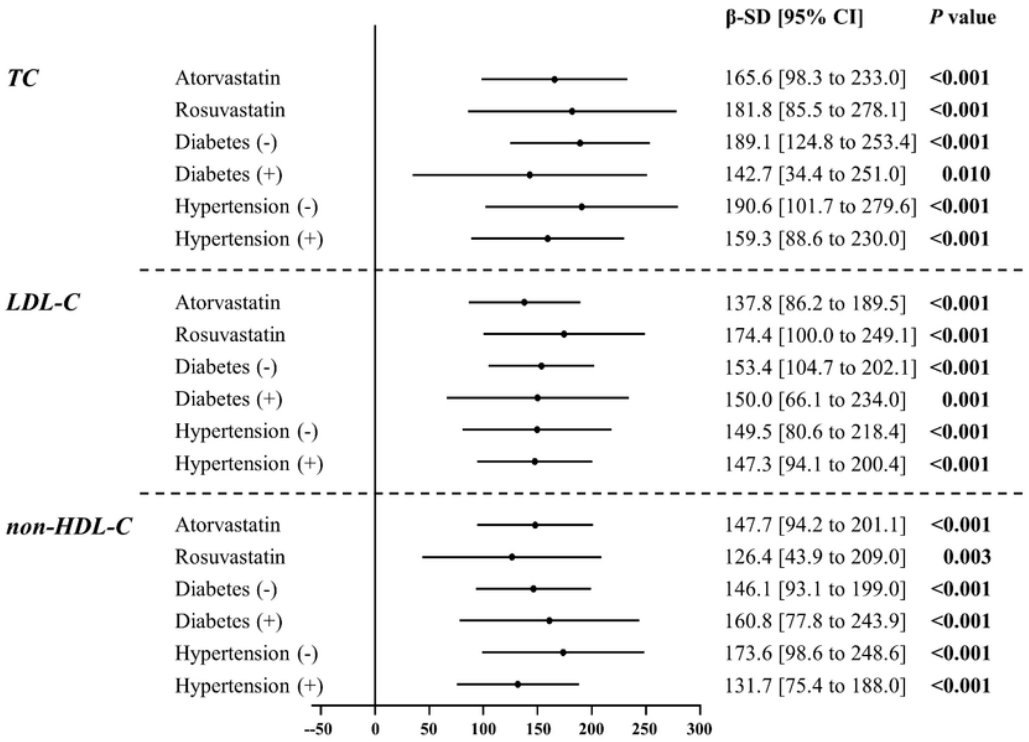

Figure 2

Forest plot of the coefficients of combination therapy (vs. intensive therapy) for SD in multivariate linear regression (95% confidence interval) by subgroup. TC=total cholesterol, LDL-C=low-density lipoprotein cholesterol, non-HDL-C=non-high-density lipoprotein cholesterol.

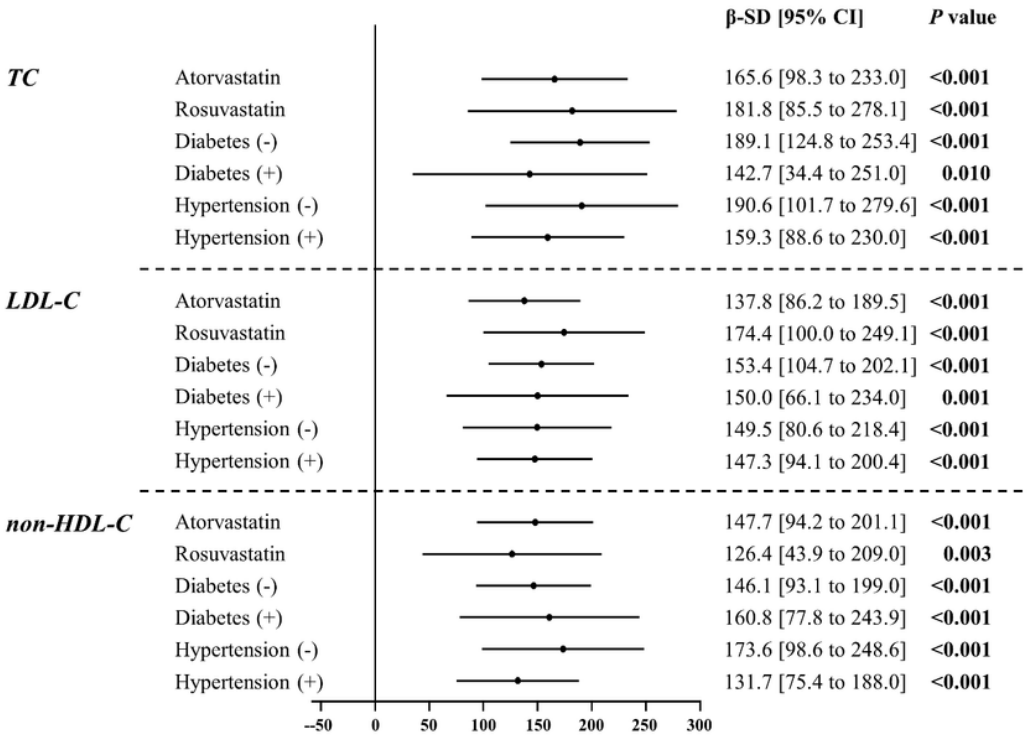

Figure 3

Forest plot of the coefficients of combination therapy (vs. intensive therapy) for CV in multivariate linear regression (95% confidence interval) by subgroup. TC, LDL-C,and non-HDL-C were the same as Figure 2.

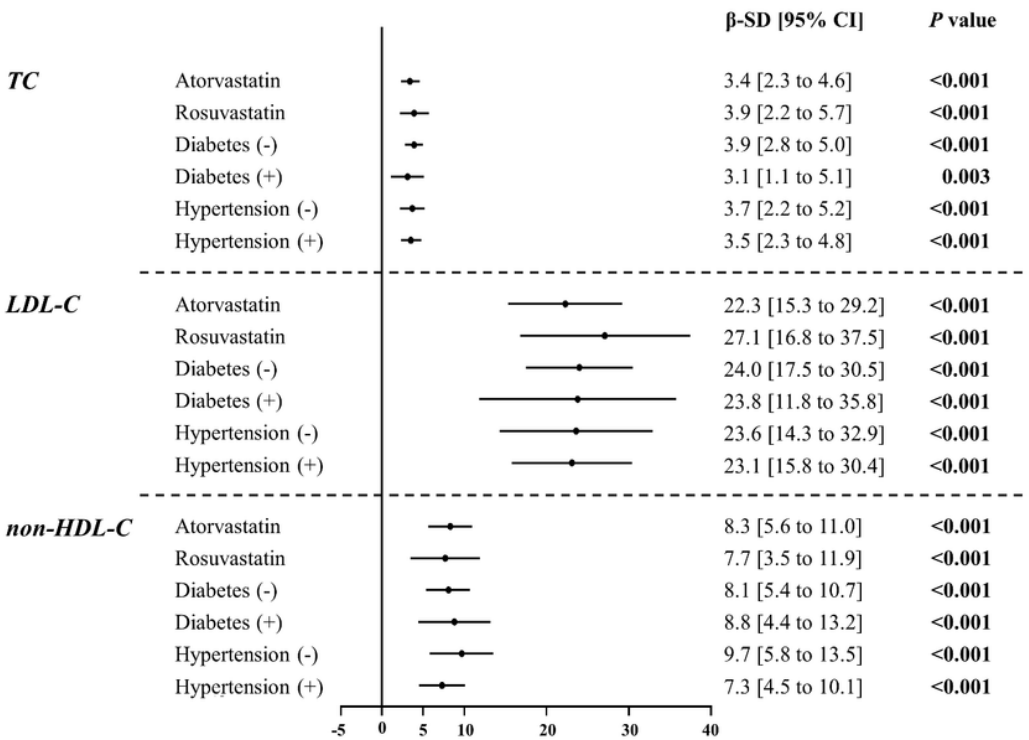

Figure 4

Forest plot of the coefficients of combination therapy (vs. intensive therapy) for VIM in multivariate linear regression (95% confidence interval) by subgroup. TC, LDL-C,and non-HDL-C were the same as Figure 2.