Intensive statin *versus* low-dose statin + ezetimibe treatment for fibrous cap thickness of coronary vulnerable plaques

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Abstract

Background: Acute coronary syndromes mainly result from abrupt thrombotic occlusion caused by atherosclerotic vulnerable plaques (VPs) that suddenly rupture or erosion. Fibrous cap thickness (FCT) is a major determinant of the propensity of a VP to rupture and is recognized as a key factor. The intensive use of statins is known to have the ability to increase FCT; however, there is a risk of additional adverse effects. However, lower dose statin with ezetimibe is known to be tolerable by patients. The present study aimed to investigate the effect of intensive statin *vs.* low-dose stain + ezetimibe therapy on FCT, as evaluated using optical coherence tomography.

Method: Patients who had VPs (minimum FCT <65 μm and lipid core $>90°$) and deferred from intervention in our single center from January 2014 to December 2018 were included in the trial. They were divided into the following two groups: intensive statin group (rosuvastatin 15–20 mg or atorvastatin 30–40 mg) and combination therapy group (rosuvastatin 5–10 mg or atorvastatin 10–20 mg + ezetimibe 10 mg). At the 12-month follow-up, we compared the change in the FCT (ΔFCT%) between the two groups and analyzed the association of ΔFCT% with risk factors. Fisher exact test was used for all categorical variables. Student's *t* test or Mann-Whitney *U*-test was used for analyzing the continuous data. The relationship between ΔFCT% and risk factors was analyzed using linear regression analysis.

Result: Total 53 patients were finally enrolled, including 26 patients who were in the intensive statin group and 27 who were in the combination therapy group. At the 12-month follow-up, the serum levels of total cholesterol (TC), total triglyceride, low-density lipoprotein (LDL-C), hypersensitive C-reactive protein (hs-CRP), and lipoprotein-associated phospholipase A2 (Lp-PLA2) levels were reduced in both the groups. The ΔTC%, ΔLDL-C%, and ΔLp-PLA2% were decreased further in the combination therapy group. FCT was increased in both the groups (combination treatment group *vs.* intensive statin group: 128.89 ± 7.64 *vs.* 110.19 ± 7.00 μm, $t = -9.282$, $P < 0.001$) at the 12-month follow-up. The increase in ΔFCT% was more in the combination therapy group ($123.46\% \pm 14.05\%$ *vs.* $91.14\% \pm 11.68\%$, $t = -9.085$, $P < 0.001$). Based on the multivariate linear regression analysis, only the serum Lp-PLA2 at the 12-month follow-up ($B = -0.203$, $t = -2.701$, $P = 0.010$), ΔTC% ($B = -0.573$, $t = -2.048$, $P = 0.046$), and Δhs-CRP% ($B = -0.302$, $t = -2.963$, $P = 0.005$) showed an independent association with ΔFCT%.

Conclusions: Low-dose statin combined with ezetimibe therapy maybe provide a profound and significant increase in FCT as compared to intensive statin monotherapy. The reductions in Lp-PLA2, ΔTC%, and Δhs-CRP% are independently associated with an increase in FCT.

Keywords: Statins; Ezetimibe; Fibrous cap thickness; Coronary vulnerable plaques; Optical coherence tomography

Introduction

Acute coronary syndromes mainly result from abrupt thrombotic occlusion based on atherosclerotic vulnerable plaques (VPs) that rupture or erode suddenly.[1-2] In general, the pathological features of VP involve the following: thin fibrous cap, large lipid core, macrophage infiltration, expansive remodeling, neovascularization, and others.[3-6] It is noteworthy that plaques with thinner fibrous cap and larger lipid necrotic core are recognized as a distinct type of VP, termed thin cap fibroatheroma (TCFA).[3-6] The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) demonstrated that TCFA was closely correlated to major adverse cardiovascular events, especially when the cap thickness was <65 μm.[4] Fibrous cap thickness (FCT) is a major determinant of plaque instability and propensity for rupture or erosion[7]; thus, increase in FCT is critical in stabilizing VPs.

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Statins are known to have the ability of stabilizing plaques and inducing an increase in the FCT, especially following intensive statin treatment.[8-11] Nevertheless, high-dose statin can also cause more adverse effects, such as myalgia, increase in the levels of hepatic enzymes, and new-onset diabetes, particularly in patients from East Asian countries, such as China.[12,13] Ezetimibe is a drug that can decrease the plasma cholesterol levels by lowering cholesterol absorption from the small intestine. When used in combination with statins, it can induce a further reduction of 6% to 25% in the low-density lipoprotein (LDL-C) level, and has shown better tolerance in patients as compared to a double dose of statin.[14] Nevertheless, to our knowledge, whether the combination therapy is superior to intensive statin monotherapy in increasing the FCT of VPs has not been systemically investigated.

The present study retrospectively investigated the effect of intensive statin *vs.* that of low-dose statin combined with ezetimibe therapy on the progression of the FCT of VPs, as assessed using optical coherence tomography (OCT).

Methods

Ethical approval

This was a retrospective single center study that was performed with the patients' written informed consents and approval by the local ethics committee of the Nanjing First Hospital.

Patients

Inclusion criteria

Patients (aged ≥18 years and ≤80 years) had VPs (OCT showed that the target lesion had a minimum FCT <65 μm and lipid core >90°) and deferred from intervention at our single center (Department of Cardiology, Nanjing First Hospital) from January 2014 to December 2018. They had hypercholesterolemia (LDL-C >1.8 mmol/L), and their lipid-lowering drugs only involved intensive statin (rosuvastatin 15–20 mg or atorvastatin 30–40 mg) or low-dose statin + ezetimibe (rosuvastatin 5–10 mg or atovastatin 10–20 mg + ezetimibe 10 mg) for at least a year. Moreover, patients should had undergone coronary angiography (CAG) and OCT examination at the 12-month follow-up.

Exclusion criteria

Myocardial infarction within the previous one month; left ventricular ejection fraction <40%; detection of thrombus in the target vessel on OCT examination; severe stenosis, tortuosity, and calcification at the target lesions; acute inflammation; infection; and pregnancy were the exclusion criteria.

Variables and OCT data collection

Information on clinical presentations, plasma biomarkers, as well as characteristics during CAG and OCT examination were collected using medical records and angiographic reviews.

Target VP was defined as a thin fibrous cap (minimum FCT <65 μm) and a large lipid core (>90°). For each cross section, the lumen area, lumen diameter, and FCT were evaluated at every 1-mm longitudinal interval. When there were ≥2 TCFAs, the one with the minimum FCT was considered the target VP. The FCT was measured twice, and the average value was considered for the final result.

OCT imaging was performed using a FD-OCT (ILUMIEN OPTIS OCT system, Abbott Vascular, Santa Clara, CA, USA). Images were acquired at 15 frames per second and digitally archived. The OCT images were analyzed using proprietary off-line review system (OPTIS[TM] Metallic Stent Optimization Software-ORW Version, Abbott Vascular, CA, USA) at the core laboratory (Nanjing Cardiovascular Center, Nanjing First Hospital, Nanjing, China). At least two independent cardiologists needed to be in agreement about the results.

Statistical analyses

Categorical variables are presented as frequencies, and comparisons were performed using Fisher exact test. Student's t test was used for comparing normally distributed continuous data, and the Mann-Whitney U-test was used for comparing non-normal continuous data. The data are presented as mean ± standard deviation or median (Q1, Q3). The relationship between the ΔFCT% and other factors was investigated using linear regression analysis. First, univariate linear regression analysis was used to investigate the association of every possible risk factor [age, hypertension, diabetes, smoking, total cholesterol (TC), total triglyceride (TG), LDL-C, hypersensitive C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2) at baseline and at the 12-month follow-up] and ΔFCT%. Thereafter, the variables with P value < 0.10 were used in the multivariate linear regression analysis. Computations were performed with SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). A P value < 0.05 was considered statistically significant.

Results

Patient population

Total 53 patients were finally enrolled from January 2014 to December 2018 at the Department of Cardiology, Nanjing First Hospital. Based on their lipid-lowering drug treatments, they were divided into the following two groups: 26 patients were allocated to the intensive statin group (among them, 20 patients received rosuvastatin 20 mg or atorvastatin 40 mg, four reduced their rosuvastatin dose from 20 mg to 15 mg, and two lowered their atorvastatin dose from 40 mg to 30 mg after 1–3 months owing to myalgia caused by a higher dose of statin), and 27 were allocated to the combination therapy group (rosuvastatin 5–10 mg or atorvastatin 10–20 mg + ezetimibe 10 mg). As per the guidelines for the Prevention and Treatment of Dyslipidemia in Chinese Adults (2016), the maximum dose of rosuvastatin is 20 mg and that for atorvastatin is 40 to 80 mg per day in China; however, due to inexperience, atorvastatin 80 mg/day is not recommended regularly.[13] All the subjects

Table 1: Baseline clinical characteristics between intensive statin treatment group and low-dose statin combined with ezetimibe therapy group.

Characteristics	Intensive statin group ($n = 26$)	Combination therapy group ($n = 27$)	Statistics	P
Age (years)	64.31 ± 8.53	63.56 ± 7.50	0.341	0.734
Male	20 (76.9)	19 (70.4)	Fisher	0.757
Hypertension	20 (76.9)	20 (74.1)	Fisher	1.000
Diabetes mellitus	9 (34.6)	7 (25.9)	Fisher	0.559
Smoking	16 (61.5)	13 (48.1)	Fisher	0.412
Medication after CAG				
Aspirin	25 (96.2)	27 (100)	Fisher	0.491
Clopidogrel	15 (57.7)	19 (70.4)	Fisher	0.398
Ticagrelor	11 (42.3)	8 (29.8)	Fisher	0.398
β Blocker	14 (53.8)	15 (55.6)	Fisher	1.000
ACEI/ARB	13 (50.0)	13 (48.1)	Fisher	1.000
Target vessel				
LAD	9 (34.6)	8 (29.6)	Fisher	0.773
LCX	8 (30.8)	8 (29.6)	Fisher	1.000
RCA	9 (34.6)	11 (40.7)	Fisher	0.779

Data are presented as n (%) or mean ± standard deviation, respectively. The differences of quantitative indexes or categorical variables between the two groups were analyzed using Student's t test or Fisher test. ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor inhibitor; LAD: Left anterior descending branch; LCX: Left circumflex artery; RCA: Right coronary artery.

received the above therapy for at least 1 year. OCT examinations were performed at baseline and at the 12-month follow-up.

Baseline clinical characteristics

There were no significant differences in the clinical characteristics (age, history of hypertension, diabetes mellitus, current smoking, medications, and distribution of target lesions) at baseline between the two groups ($P > 0.05$) [Table 1].

Laboratory results

There were no significant differences in the levels of aspartate aminotransferase, creatine kinase, TC, TG, LDL-C, high-density lipoprotein (HDL-C), hs-CRP, and Lp-PLA2 at baseline ($P > 0.05$).

The serum TC, TG, LDL-C, hs-CRP, and Lp-PLA2 levels were reduced at the 12-month follow-up in both groups. Among them, only LDL-C and Lp-PLA2 levels were significantly different between the two groups (the combination therapy group vs. intensive statin group: LDL-C, 1.36 ± 0.19 vs. 1.46 ± 0.15 mmol/L, $t = 2.132$, $P = 0.038$; Lp-PLA2, 162.00 [145.00, 175.00] vs. 187.00 [157.00, 215.00] ng/mL, $t = 3.907$, $P < 0.001$).

There were no significant differences in the ΔTG%, ΔHDL-C%, and Δhs-CRP% between the two groups ($P > 0.05$); however, ΔTC%, ΔLDL-C%, and ΔLp-PLA2% were decreased further in the combination therapy group and were listed as follows (combination treatment group vs. intensive statin group: −26.17 [−27.56, −21.54]% vs. −21.44 [−23.24, −18.35]%, $t = 3.548$, $P = 0.001$; −[51.36 ± 7.05]% vs. −[45.63 ± 5.80]%, $t = 3.225$, $P = 0.002$; −33.92 [−42.02,−20.66]% vs. −30.09 [−34.81,−12.90]%, $t = 2.110$, $P = 0.040$) [Table 2].

OCT findings

There were no significant differences in the FCT, lipid core angle (LCA), minimum lumen diameter (MLD), and minimum lumen area (MLA) at baseline between the two groups ($P > 0.05$).

The FCT was increased in both the groups (the combination treatment group vs. the intensive statin group: 128.89 ± 7.64 vs. 110.19 ± 7.00 μm, $t = −9.282$, $P < 0.001$) at the 12-month follow-up, and the ΔFCT% increased more in the combination therapy group (123.46% ± 14.05% vs. 91.14% ± 11.68%, $t = −9.085$, $P < 0.001$) [Figures 1 and 2].

The LCA was decreased at the 12-month follow-up in both the groups; there was no significant difference in the ΔLCA% of the two groups ($P > 0.05$).

MLD and MLA seemed larger at the 12-month follow-up compared to those at baseline; however, there were no significant differences between the two groups ($P > 0.05$) [Table 3].

The association of △FCT% and risk factors:

From the univariate linear regression analysis (including age, history of hypertension, diabetes mellitus, current smoking, TC, TG, LDL-C, hs-CRP, Lp-PLA2 at baseline, Lp-PLA2 at the 12-month follow-up, ΔTC%, ΔTG%, ΔLDL-C%, Δhs-CRP%, and ΔLp-PLA2%), serum TC ($B = −18.293$, $t = −3.374$, $P = 0.001$), LDL-C ($B = −38.850$, $t = −2.759$, $P = 0.008$), Lp-PLA2 ($B = −0.136$, $t = 2.127$, $P = 0.038$) at the 12-month follow-up, ΔTC% ($B = −1.350$, $t = −3.402$, $P = 0.001$), and Δ hs-CRP% ($B = −0.179$, $t = −1.808$, $P = 0.076$) were associated with the ΔFCT%.

Table 2: Laboratory results at baseline and 12-month follow-up between intensive statin treatment group and low-dose statin combined with ezetimibe therapy group.

Variables	Intensive statin group (n = 26)	Combination therapy group (n = 27)	Statistics	P
AST (U/L)				
Baseline	20.00 (12.00, 28.00)	20.00 (15.00, 32.00)	0.105	0.917
Follow-up	30.00 (21.00, 34.00)	22.00 (20.00, 27.00)	1.576	0.121
CK (U/L)				
Baseline	75.00 (58.00, 97.00)	93.00 (68.00, 134.00)	−1.292	0.203
Follow-up	89.00 (72.00, 100.00)	98.00 (78.00, 134.00)	−1.071	0.289
TC (mmol/L)				
Baseline	4.30 ± 0.45	4.42 ± 0.81	−0.668	0.508
Follow-up	3.40 ± 0.32	3.25 ± 0.54	1.217	0.230
ΔTC%	−21.44 (−23.24, −18.35)	−26.17 (−27.56, −21.54)	3.548	0.001
TG (mmol/L)				
Baseline	1.59 ± 0.78	1.83 ± 0.87	−1.076	0.287
Follow-up	1.47 ± 0.74	1.72 ± 0.80	−1.192	0.239
ΔTG%	−6.50 (−9.64, −3.14)	−5.97 (−7.89, −2.52)	−0.663	0.511
LDL-C (mmol/L)				
Baseline	2.71 ± 0.39	2.86 ± 0.68	−1.034	0.307
Follow-up	1.46 ± 0.15	1.36 ± 0.19	2.132	0.038
ΔLDL-C%	−(45.63 ± 5.80)	−(51.36 ± 7.05)	3.225	0.002
HDL-C (mmol/L)				
Baseline	0.96 ± 0.25	1.00 ± 0.19	−0.575	0.568
Follow-up	1.03 ± 0.22	1.05 ± 0.17	−0.285	0.777
ΔHDL-C%	7.84 (2.26, 13.16)	3.45 (2.25, 6.67)	1.849	0.070
hs-CRP (μg/mL)				
Baseline	1.84 (1.22, 2.56)	1.89 (1.18, 5.26)	−0.846	0.401
Follow-up	1.64 (1.35, 1.89)	1.38 (1.02, 1.88)	−0.161	0.873
Δhs-CRP%	−10.34 (−37.71, −2.56)	−27.09 (−46.42, −6.25)	1.593	0.117
Lp-PLA2 (ng/mL)				
Baseline	255.40 (177.88, 328.00)	224.00 (200.00, 325.00)	0.377	0.708
Follow-up	187.00 (157.00, 215.00)	162.00 (145.00, 175.00)	3.907	<0.001
ΔLp-PLA2%	−30.19 (−34.81, −12.90)	−33.92 (−42.02, −20.66)	2.110	0.040

Data are presented as mean ± standard deviation or median (Q1, Q3), respectively. The differences of quantitative indexes or categorical variables between the two groups were analyzed using Student's t test and Mann-Whitney U test. Δ%: (Value of follow-up–value of baseline)/value of baseline. AST: Aspartate aminotransferase; CK: Creatine kinase; TC: Total cholesterol; TG: Total triglyceride; LDL-C: Low-density lipoprotein; HDL-C: High-density lipoprotein; hs-CRP: Hypersensitive C-reactive protein; Lp-PLA2: Lipoprotein-associated phospholipase A2.
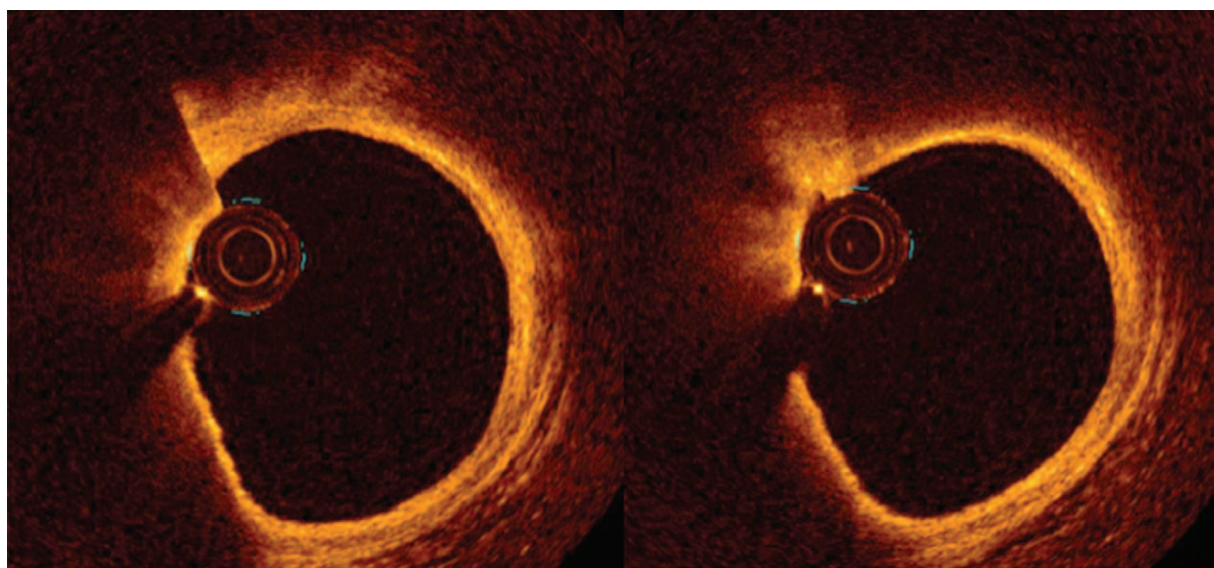

Figure 1: The minimum fibrous cap thickness was 50 μm at baseline in the intensive statin group (left); the minimum fibrous cap thickness was increased to 110 μm at the 12-month follow-up in the intensive statin group (right).
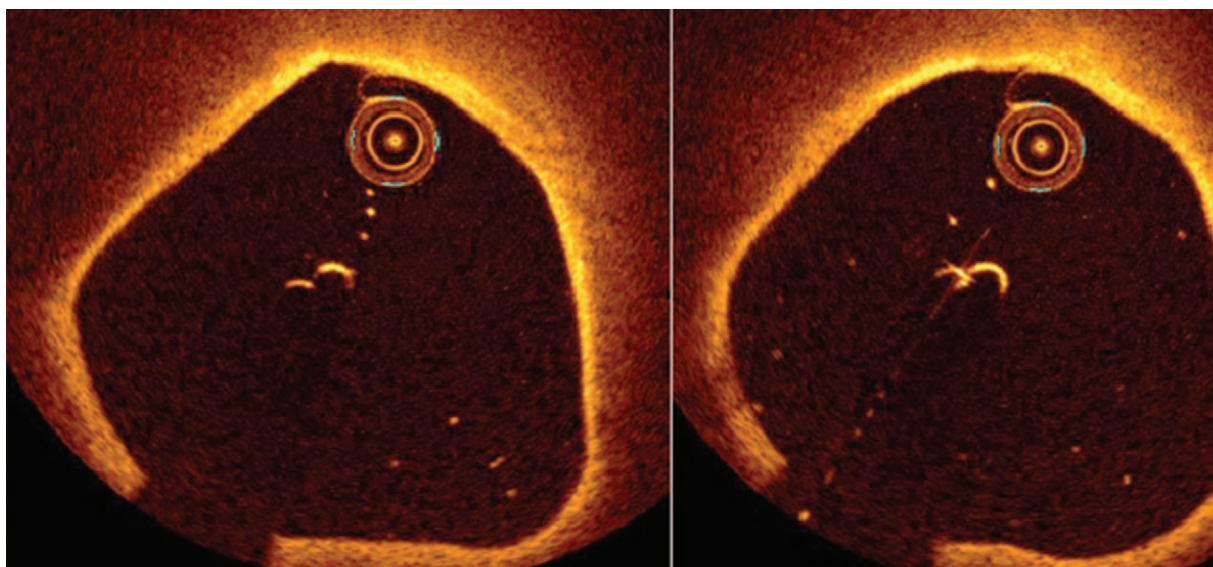
Figure 2: The minimum fibrous cap thickness was 60 μm at baseline in the combination therapy group (left); the minimum fibrous cap thickness was increased to 140 μm at the 12-month follow-up in the combination therapy group (right).

Table 3: OCT measurements at baseline and at the 12-month follow-up between the intensive statin treatment group and the low-dose statin combined with ezetimibe therapy group.

Variables	Intensive statin group ($n = 26$)	Combination therapy group ($n = 27$)	Statistics	P
FCT (μm)				
Baseline	57.69 ± 2.54	58.89 ± 2.12	−1.858	0.069
Follow-up	110.19 ± 7.00	128.89 ± 7.64	−9.282	<0.001
ΔFCT%	91.14 ± 11.68	123.46 ± 14.05	−9.085	<0.001
LCA (°)				
Baseline	174.81 ± 19.26	181.48 ± 16.92	−1.342	0.186
Follow-up	155.00 ± 15.23	156.11 ± 14.03	−0.276	0.783
ΔLCA%	−10.53 (−12.50, −9.09)	−8.82 (−21.05, −7.90)	1.665	0.102
MLD (mm)				
Baseline	2.53 ± 0.24	2.55 ± 0.28	−0.326	0.746
Follow-up	2.62 ± 0.22	2.65 ± 0.29	−0.337	0.737
MLA (mm^2)				
Baseline	5.07 ± 0.96	5.18 ± 1.11	−0.386	0.701
Follow-up	5.44 ± 0.91	5.57 ± 1.16	−0.434	0.666

Data are presented as mean ± standard deviation or median (Q1, Q3), respectively. The differences of quantitative indexes or categorical variables between the two groups were analyzed by Student's *t* test and Mann-Whitney *U* test. Δ%: (Value of follow-up–value of baseline)/value of baseline. FCT: Fibrous cap thickness; LCA: Lipid core angle; MLD: Minimum lumen diameter; MLA: Minimum lumen area.

From multivariate linear regression analysis (including TC, LDL-C, Lp-PLA2 at 12-month follow-up and ΔTC %, Δhs-CRP%), only serum Lp-PLA2 at the 12-month follow-up ($B = -0.203$, $t = -2.701$, $P = 0.010$) and the **ΔTC%** ($B = -0.573$, $t = -2.048$, $P = 0.046$), Δhs-CRP% ($B = -0.302$, $t = -2.963$, $P = 0.005$) showed an independent association with ΔFCT% [Table 4].

Discussion

The study retrospectively investigated the effect of intensive statin compared to that of low-dose statin combined with ezetimibe in VP progression as evaluated using OCT. The FCT was increased more in the low-dose statin combined with ezetimibe therapy group, and ΔFCT % was associated with the change in the serum lipid and inflammatory factor levels.

FCT is an important determinant of plaque instability[7,15]; the PROSPECT study showed that when the minimum FCT was <65 μm, it could rupture.[4] Statins have the ability to stabilize plaques and induce the regression of coronary atherosclerosis; further, they exert pleiotropic effects, such as anti-inflammation and endothelial function improvement especially in high-dose therapy.[16-19] Several studies have shown that statin therapy can increase the FCT by reducing the plasma LDL-C level.[10,20] The

Table 4: Association of ∆FCT% and risk factors.

Model	B	t	P
TC (follow-up)	−8.617	−1.143	0.259
∆TC%	−0.573	−2.048	0.046
LDL-C (follow-up)	−1.747	−0.087	0.931
∆hs-CRP%	−0.302	−2.963	0.005
Lp-PLA2 (follow-up)	−0.203	−2.701	0.010

Linear regression analysis was used for assessing the association of ∆FCT% and risk factors (TC, LDL-C, Lp-PLA2 at the 12-month follow-up and ∆TC%, ∆hs-CRP% from baseline to 12-month follow-up); ∆%: (Value of follow-up–value of baseline)/value of baseline. TC: Total cholesterol; LDL-C: Low-density lipoprotein; hs-CRP: Hypersensitive C-reactive protein; Lp-PLA2: Lipoprotein-associated phospholipase A2.

∆FCT% was increased more in the intensive statin group than in the lower dose statin group.[8,10,21] The Effect of PitavaStatin on Coronary Fibrous cap Thickness-Assessment by Fourier-Domain Optical CoheRence Tomography study showed that if statins were used earlier, FCT increased more.[22] The Effect of AtorvaStatin therapY on FIbrous cap Thickness study on coronary atherosclerotic plaque, as assessed with OCT showed that statins increased the FCT and reduced the accumulation of macrophages; the advantages were more obvious in the higher dose statin treatment than in the lower dose statin treatment.[8] However, in our country, most patients are unable to tolerate high-dose statin owing to its dose-dependent adverse effects, such as myalgia and liver dysfunction.[13] Thus, there is a need for additional therapies. Ezetimibe can lower the plasma cholesterol level by reducing cholesterol absorption from the small intestine; the combination of ezetimibe and statin therapy was widely used owing to its superior effect in terms of reduction in the LDL-C and lower prevalence of adverse effects.[23] However, whether the combination therapy had a superior effect on stabilizing coronary VP, especially increasing the FCT remains unclear.[24-26] Few studies have evaluated the effect of combination therapy on the FCT of VPs. One study showed that when ezetimibe was combined with statin, it could further increase the FCT more than statin monotherapy[27]; this finding is similar to our result. However, why it is superior to intensive statin therapy? This might be attributable to a further reduction in the lipid levels and inflammatory factor levels because of combination therapy. Plasma lipid levels and inflammation are major risk factors of plaque instability[28-30]; the resolution of these two indicators is crucial for the stabilization of VP. When ezetimibe was combined with a lower dose stain, it could achieve a similar or lower reduction in the lipid percentage than intensive statin therapy, and it had good tolerance in most Chinese patients. However, whether ezetimibe monotherapy exerts an anti-inflammatory effect remains controversial.[31-35] Several studies have shown that ezetimibe monotherapy could decrease CRP, while in combination with statin, it caused additional reduction in CRP.[31-32] The Improved Reduction of Outcomes: Vytorin Efficacy International Trial study showed a further decrease in CRP when added to statins therapy.[14] However, it is unclear whether these additional benefits are related to further lipid reduction or other mechanisms of ezetimibe that accentuate these effects when combined with statins. A previous study found that ∆FCT% may be related to the reduction in TC, LDL-C, and hs-CRP,[27] comparable to our results. However, our sample size was relatively small; therefore, larger, randomized registry studies are required to confirm our findings.

This was a retrospective, observational study that employed a relatively small sample and had a selection bias of the enrolled patients. Thus, these findings strongly suggest the need for a larger, randomized registry study to validate our findings.

The present results suggest that low-dose statin combined with ezetimibe therapy could cause a profound and significant increase in the FCT as compared to intensive statin monotherapy. The decrease in the Lp-PLA2, ∆TC%, and ∆hs-CRP% was independently associated with increased FCT. Thus, low-dose statin combined with ezetimibe therapy may be a better choice for stabilizing VP as compared to intensive statin therapy.

Funding

Conflicts of interest

None.

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