Observational Study

Effects of different statins application methods on plaques in patients with coronary atherosclerosis

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Abstract

BACKGROUND
Discontinued application of statins may be related to adverse cardiovascular events. However, it is unclear whether different statins administration methods have effects on coronary artery plaques.

AIM
To evaluate the effects of different statins application methods on plaques in patients with coronary atherosclerosis.

METHODS
A total of 100 patients diagnosed with atherosclerotic plaque by coronary artery computed tomography were continuously selected and divided into three groups according to different statins administration methods (discontinued application group, n = 32; intermittent application group, n = 39; sustained application group, n = 29). The effects of the different statins application methods on coronary atherosclerotic plaque were assessed.

RESULTS
The volume change and rate of change of the most severe plaques were significantly reduced in the sustained application group (P ≤ 0.001). The volume change of the most severe plaques correlated positively with low-density lipoprotein (LDL-C) levels only in the sustained application group (R = 0.362, P = 0.013). There were no changes in plaques or LDL-C levels in the intermittent and discontinued application groups.

CONCLUSION
Continuous application of statins is effective for controlling plaque progression,
Administering statins is an important measure for preventing atherosclerotic diseases. Many studies have confirmed that long-term application of statins can reduce cardiovascular events and improve the prognosis of coronary heart disease[19]. This effect is mainly related to the abilities of statins to lower cholesterol and stabilize or reverse coronary artery plaque volume (CAPV)[4-7]. A series of intravascular ultrasound studies have also found that lipid-lowering therapy with statins can achieve CAPV reduction[8-9]. However, it is undeniable that in a large number of clinical trials, strict application control was performed for statins, whereas in clinical practice, the application of statins has a very high clinical discontinuation rate[10]. It is believed that the natural withdrawal rate of statins is approximately 30% in the general population[11] and that the discontinuation rate in the first year is as high as 40%-75%[12], regardless of the type of statins[13]. In theory and practice, it is recognized that the cardiovascular benefit of statins depends on their compliance[14]. Overall, discontinued application of statins may be closely related to the occurrence of adverse cardiovascular events[15-16], and adverse events caused by discontinuation are more severe than those in patients who have never taken statins[17]. Although previous studies have found that different ways of administering statins may affect the occurrence of cardiovascular events, it is unclear whether different statins administration methods have effects on coronary artery plaques. Therefore, the main purpose of this study was to analyse the effects of different statins application methods on coronary artery plaques.

**MATERIALS AND METHODS**

**General information**

A total of 100 patients in our hospital who were confirmed as having definitive coronary atherosclerotic plaques by 256-row coronary computed tomography angiography (CCTA) were continuously selected from September 2011 to November 2012. These patients were all prescribed statins and did not have definite myocardial ischaemia. The specific type and dose of statins were not limited. Diagnosis of plaques...
by CCTA and the inclusion criteria were as follows: Non-calcified and/or mixed plaques with a length of ≥ 5 mm and a degree of luminal stenosis < 50%. All enrolled patients were treated with statins, and the baseline level of low-density lipoprotein (LDL) was not limited. The exclusion criteria were as follows: Known coronary heart disease; heart failure; uncontrollable hypertension; liver and kidney dysfunction; inflammatory or immune disease in the active phase; poor-quality coronary artery images; coronary artery calcification score (CACS) ≥ 400; body weight index ≥ 40 kg/m². The study was approved by the ethics committee of the First Affiliated Hospital of China Medical University.

**Research methods**

Blood biochemical tests, including blood lipids, blood sugar, and liver and kidney function, were performed before the CCTA examination. All patients were followed for 1 year after enrollment on a monthly basis. During the follow-up, the use of medications and major adverse cardiovascular events (MACE) were recorded, including definitive angina, cardiogenic death, non-fatal myocardial infarction, revascularization treatment and stroke, and readmission due to cardiovascular events. At the end of follow-up, blood biochemical tests and CCTA were performed again. The patients were divided into three groups according to the application of statins during the follow-up: Group I (discontinued application of statins, patients who discontinued taking statins during follow-up); Group II (intermittent application of statins, patients who suspended and then re-started statins during the follow-up; the intermittent retake occurred at least twice, and the intermittent retake lasted at least 1 mo); Group III (sustained application of statins, patients who continuously took statins during the follow-up).

**Image analysis**

All scans were evaluated on computer 3D workstations, and CACS measurements were performed using the integration system proposed by Agatston et al[21]. Coronary artery images with artefacts and those which did not allow for assessing the extent of the lesion and the nature of the plaque were excluded from the study. A 16-segment coronary artery tree model was used for analysis[22]. The cross-section perpendicular to the vascular centreline was further reconstructed. On axial, coronal, and/or sagittal images, the cross-section moved 0.3/0.4 mm each time at the site of the plaque with reconstructed blood vessels, and the vascular and lumen area of each cross-section was measured.

The calculation formulas applied in our study are as follows: Plaque volume = total vessel volume - total lumen volume; plaque volume percentage = [(total vessel volume - total lumen volume)/total vessel volume] × 100%; percent change in plaque volume = plaque volume percentage at the end of follow-up - plaque volume percentage at baseline; most severe plaque volume (5 mm) = blood vessel volume at the most severe lesion (5 mm) - lumen volume at the most severe lesion (5 mm); the most severe plaque volume (5 mm) refers to the volume of the 5-mm-long plaque measured at the most severe lesion at baseline, and the calculation of the percentage and percentage change of the most severe plaque volume (5 mm) are the same as that of the plaque volume. The vascular remodelling index of all lesions was recorded.

All plaques were divided into three types according to their compositions: Calcified, non-calcified, and mixed. If the radiation density of the plaque is higher than the lumen density, it is calcified; if the radiation density is higher than the adjacent soft tissue and lower than the lumen, it is non-calcified. Calcified plaque means that the calcified tissue in the plaque exceeds 75% of the area, non-calcified plaque means that the calcified tissue in the plaque is less than 25%, and mixed plaque means that the calcified tissue is between 25% and 75%[23]. In this study, changes in non-calcified and mixed plaques were assessed by volume and in calcified plaques by CACS.

**Statistical methods**

The enumeration data of the baseline characteristics are expressed as absolute values and percentages; measurement data are expressed as the mean ± SD. Measurement data were compared by analysis of variance, and enumeration data were analysed by the chi-square test. Correlation between the percent change in the most disease (5 mm CAPV) and percent change in LDL-C in the different patterns of statins use was analyzed by liner regression analysis. SPSS 21.0 was used for all statistical analyses. P < 0.05 was considered statistically significant.
RESULTS

Basic data
All 100 selected patients completed the follow-up, and there were no significant differences in their baseline characteristics (see Table 1 for details).

Blood lipids and medication applications
At the end of follow-up, the LDL-C and total cholesterol (TC) levels of group III were significantly lower than those of the other two groups ($P < 0.01$). In group III, changes in LDL-C, high-density lipoprotein, and TC levels were significantly higher than those of the other two groups ($P < 0.05$; Table 2). The medication applications during the follow-up of the three groups are shown in Table 3, and there were no significant differences among the groups in types of statins during follow-up.

Coronary atherosclerotic plaque changes
At baseline, there were no significant differences in the number and length of plaques among the three groups, nor were there significant differences in plaque characteristics and number of lesion vessels. And the volume of the most severe plaques among the three groups was similar, but at the end of follow-up, the volume in Group III was significantly smaller than that in the other two groups ($10.19 \pm 5.66 \text{ mm}^3$ vs $10.38 \pm 5.81 \text{ mm}^3$ vs $6.67 \pm 4.99 \text{ mm}^3$, $P = 0.001$). Compared with the other two groups, the volume percentage change of the most severe plaques in Group III was significantly reduced ($7.24\% \pm 4.95\%$ vs $6.98\% \pm 5.18\%$ vs $-3.48\% \pm 4.74\%$, $P < 0.001$). There were no significant differences in plaque changes between Group I and Group II (Table 4).

Correlation between coronary plaque changes and LDL-C changes
Correlation analysis showed that the volume percentage change of the most severe plaques (5 mm) correlated positively with the percentage change of LDL-C only in Group III ($R = 0.362$, $P = 0.013$). There were no such correlations in Group I ($R = 0.270$, $P = 0.058$) or Group II ($R = 0.081$, $P = 0.555$).

Adverse events
There were few occurrences of MACE events among the three groups. No cardiac death or myocardial infarction was observed, and no vesselization treatment occurred. There were three cases of stroke, three cases of angina, and 19 cases of re-hospitalization. Although MACE events were not significantly different among the three groups, Group III exhibited a tendency of improvement.

DISCUSSION
Atherosclerotic disease is a major condition with a high incidence that causes great harm to the population. Applying statins to control cholesterol is one of the most important preventive measures. Studies have found that taking statins caused plaque regression $^{24,25}$, but it took at least two years $^{26}$. Nevertheless, discontinuation of statin application is still very common $^{28-31}$. A study even found that discontinuation could cause a worse prognosis than never applying statins $^{20}$.

In our study, follow-ups occurred in real clinical practice to observe the effects of different statins application methods on coronary atherosclerotic plaques. Although the application duration of statins was only one year, sustained application reduced the volume of the most severe atherosclerotic plaques compared with intermittent and discontinued applications, suggesting that sustained application of statins plays an important role in treating atherosclerosis. In contrast, coronary atherosclerotic plaques showed progression in the discontinued and intermittent application groups. These results suggest that statins are effective for the intervention of atherosclerotic plaques and should be applied continuously. Intermittent application not only increases the medication cost and patient burden but also may not be effective.

Our study also found that when continuously taking statins, the retraction of coronary atherosclerotic plaques was closely related to a decrease in LDL-C level. This significant correlation only appeared with continuous administration, further showing that the effect of statins in reversing plaque is mainly related to the decrease in LDL-C level. As intermittent or discontinued application of statins makes it difficult to effectively control LDL-C level, plaque progression can still be seen on imaging.
Table 1 Baseline characteristics of the study population

| Item                        | Group I (n = 32) | Group II (n = 39) | Group III (n = 29) | P value |
|-----------------------------|-----------------|-------------------|-------------------|--------|
| Age (yr)                    | 55.56 ± 9.49    | 55.03 ± 9.35      | 58.14 ± 9.56      | 0.38   |
| Male, %                     | 68.8 (22)       | 46.2 (18)         | 14.4 (12)         | 0.07   |
| Body mass index (kg/m²)     | 24.66 ± 3.17    | 25.77 ± 3.49      | 24.34 ± 2.86      | 0.15   |
| Smoking, %                  | 40.6 (13)       | 29.2 (11)         | 20.7 (6)          | 0.23   |
| Hypertension, %             | 50.0 (16)       | 51.3 (20)         | 41.4 (12)         | 0.70   |
| Diabetes, %                 | 21.9 (7)        | 15.4 (6)          | 17.2 (5)          | 0.77   |
| Stroke history, %           | 3.1 (1)         | 2.6 (1)           | 3.4 (1)           | 0.98   |
| Follow-up period (d)        | 456.28 ± 27.86  | 460.08 ± 32.91    | 460.97 ± 33.61    | 0.82   |

Values are expressed as the mean ± SD or % (n).

Table 2 Changes in blood lipids

| Item                  | Group I (n = 32) | Group II (n = 39) | Group III (n = 29) | P value |
|-----------------------|-----------------|-------------------|-------------------|--------|
| LDL-C (mmol/L)        |                 |                   |                   |        |
| Baseline              | 2.35 ± 0.67     | 2.88 ± 1.00       | 3.17 ± 0.98       | 0.02   |
| Follow-up             | 2.72 ± 0.57     | 2.84 ± 0.71       | 2.12 ± 0.45       | < 0.001|
| Change                | 0.41 ± 0.40     | -0.04 ± 0.51      | -1.05 ± 0.75      | < 0.001|
| HDL-C (mmol/L)        |                 |                   |                   |        |
| Baseline              | 1.16 ± 2.92     | 1.34 ± 0.99       | 1.0 ± 0.29        | 1.37   |
| Follow-up             | 1.04 ± 0.22     | 1.33 ± 0.76       | 1.14 ± 0.22       | 0.08   |
| Change                | -0.12 ± 0.17    | -0.01 ± 0.29      | 0.14 ± 0.19       | < 0.001|
| TC (mmol/L)           |                 |                   |                   |        |
| Baseline              | 3.89 ± 0.73     | 4.74 ± 1.05       | 4.56 ± 1.21       | 0.04   |
| Follow-up             | 3.99 ± 0.64     | 4.64 ± 0.77       | 4.12 ± 0.83       | 0.002  |
| Change                | 0.11 ± 0.22     | -0.10 ± 0.59      | -0.33 ± 0.58      | 0.011  |
| TG (mmol/L)           |                 |                   |                   |        |
| Baseline              | 1.65 ± 0.87     | 1.09 ± 0.59       | 1.44 ± 0.95       | 0.06   |
| Follow-up             | 1.65 ± 0.53     | 1.39 ± 0.41       | 1.36 ± 0.56       | 0.08   |
| Change                | -0.02 ± 0.89    | 0.05 ± 1.27       | -0.03 ± 0.69      | 0.94   |

Values are expressed as the mean ± SD. LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TC: Total cholesterol; TG: Triglycerides.

Therefore, continuously using statins to effectively reduce LDL-C level is a very important factor in the prevention and treatment of atherosclerotic lesions. Once discontinued, the nitric oxide level will decrease below baseline\(^{32}\). Additionally, endothelial protection disappears and endothelial damage is further exacerbated after discontinuing statin treatment in patients with coronary heart disease\(^{33}\). The anti-inflammatory effects of statins were also quickly lost after discontinuation\(^{34}\). These effects were not related to LDL-C levels\(^{35}\). In our study, LDL-C levels of patients in the intermittent application group also decreased, but there was no reduction in plaque volume. Therefore, the reduction in plaque volume is not only related to reduced LDL-C level but may be also closely associated with the continuous application of statins\(^{36}\).

Although there were no significant differences in adverse cardiovascular events with the different statins application methods, the incidences in the intermittent and discontinued application groups tended to be higher than that in the sustained...
application group. In general, patients should receive effective statin intervention because early statin treatment has important clinical value. However, in real life, patients often neglect medication because they have no symptoms or discomfort. Clinicians also lack scientific and systematic managements of patients. In actual practice, doctors at different levels need to participate, and advanced instruments for a non-invasive evaluation of atherosclerosis disease should be used\[^{37}\]. The patients that we observed were close to clinical reality and reflective of statin usage in the real world. Moreover, the population was selected from an outpatient department of a tertiary hospital, yet it was difficult for most of them to continue taking the medication. Overall, the findings suggest that we should strengthen the management of patients and the promotion of patients’ health education, disease knowledge, and medication knowledge to improve patients’ medication compliance and truly improve clinical prognosis.

Our study has certain limitations: The sample size was small, and the follow-up time was relatively short. There may also be some uncertain confounding factors affecting the results. Despite these limitations, our research reflects the actual clinical situation in the real world and is of great significance for the guidance of clinical practice.

**CONCLUSION**

The persistent and continuous application of statins to reduce LDL-C level can effectively reverse plaques. The participation and management of the nursing team are also important. Indeed, through careful observation, follow-up, and education, the nursing team can play a better role in the management of such patients who require long-term medication. Nonetheless, the specific mechanism is unclear, and further research is needed.

| Item                                      | Group I (n = 32) | Group II (n = 39) | Group III (n = 29) | P value |
|--------------------------------------------|------------------|-------------------|-------------------|--------|
| Baseline                                  |                  |                   |                   |        |
| Aspirin                                   | 34.3 (11)        | 23.1 (9)          | 34.5 (10)         | 0.48   |
| β-receptor blocker                        | 15.6 (5)         | 7.7 (3)           | 20.7 (6)          | 0.30   |
| ACEI/ARB                                  | 15.6 (5)         | 10.3 (4)          | 10.3 (3)          | 0.75   |
| CCB                                       | 12.5 (4)         | 17.9 (7)          | 24.1 (7)          | 0.50   |
| Statins                                   | 9.4 (3)          | 7.7 (3)           | 13.8 (4)          | 0.70   |
| Glucose-lowering treatment                | 18.8 (6)         | 7.7 (3)           | 17.2 (5)          | 0.32   |
| Follow-up                                 |                  |                   |                   |        |
| Aspirin                                   | 28.1 (9)         | 20.5 (8)          | 34.5 (10)         | 0.43   |
| β-receptor blocker                        | 12.5 (4)         | 7.7 (3)           | 20.7 (6)          | 0.30   |
| ACEI/ARB                                  | 18.8 (6)         | 12.8 (5)          | 13.8 (4)          | 0.77   |
| CCB                                       | 12.5 (4)         | 12.8 (5)          | 17.2 (5)          | 0.84   |
| Glucose-lowering treatment                | 18.8 (6)         | 10.3 (4)          | 17.2 (5)          | 0.55   |
| Types of statins during follow-up         |                  |                   |                   | 0.27   |
| Atorvastatin                              | 46.9 (15)        | 51.3 (20)         | 58.6 (17)         |        |
| Simvastatin                               | 31.3 (10)        | 33.3 (13)         | 27.6 (8)          |        |
| Pravastatin                               | 3.1 (1)          | 0 (0)             | 3.4 (1)           |        |
| Rosuvastatin                              | 15.6 (5)         | 12.8 (5)          | 10.3 (3)          |        |
| Fluvastatin                               | 3.1 (1)          | 2.6 (1)           | 0 (0)             |        |

Values are expressed as % (n). ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker.
### Table 4 Changes of coronary plaque characteristics

| Item                                      | Group I (n = 32) | Group II (n = 39) | Group III (n = 29) | P value |
|-------------------------------------------|------------------|-------------------|--------------------|---------|
| Total number of plaques (n)               | 50               | 56                | 46                 |         |
| Number of plaques, per person             | 1.56 ± 0.62      | 1.43 ± 0.75       | 1.52 ± 0.79        | 0.70    |
| Length (mm), per plaque                   | 10.19 ± 5.12     | 9.97 ± 4.70       | 8.84 ± 3.73        | 0.32    |
| Plaque nature                             |                  |                   |                    | 0.94    |
| Non-calcified                             | 54.0 (27)        | 57.1 (32)         | 56.5 (26)          |         |
| Mixed                                     | 46.0 (23)        | 42.9 (24)         | 43.5 (20)          |         |
| Lesion number                             |                  |                   |                    | 0.65    |
| Single-vessel                             | 53.1 (17)        | 64.1 (25)         | 62.1 (18)          |         |
| Double-vessel                             | 31.3 (10)        | 30.8 (12)         | 27.6 (8)           |         |
| Triple-vessel/left main                   | 15.6 (5)         | 5.1 (2)           | 10.3 (3)           |         |
| Most severe plaque volume (5 mm), per plaque |                  |                   |                    |         |
| Baseline, mm³                              | 8.18 ± 5.82      | 8.34 ± 5.31       | 8.03 ± 5.48        | 0.96    |
| Follow-up, mm³                             | 10.19 ± 5.66     | 10.38 ± 5.81      | 6.67 ± 4.99        | 0.001   |
| Plaque volume change, mm³                 | 2.01 ± 1.02      | 2.03 ± 1.35       | -1.36 ± 1.94       | < 0.001 |
| Plaque volume percentage change, %        | 7.24 ± 4.95      | 6.98 ± 5.18       | -3.48 ± 4.74       | < 0.001 |
| Plaque volume, per plaque                 |                  |                   |                    |         |
| Baseline, mm³                              | 14.79 ± 11.11    | 14.76 ± 11.97     | 11.28 ± 9.53       | 0.29    |
| Follow-up, mm³                             | 17.82 ± 16.75    | 17.41 ± 13.58     | 9.58 ± 7.95        | 0.002   |
| Plaque volume change, mm³                 | 3.09 ± 2.93      | 2.64 ± 3.12       | -1.79 ± 3.04       | < 0.001 |
| Plaque volume percentage change, %        | 5.38 ± 6.09      | 5.05 ± 4.82       | -2.04 ± 3.68       | < 0.001 |
| CACS                                       |                  |                   |                    |         |
| Baseline                                   | 41.22 ± 55.04    | 45.44 ± 31.82     | 101.00 ± 210.44    | 0.40    |
| Follow-up                                  | 51.72 ± 65.76    | 56.78 ± 35.18     | 114.45 ± 229.93    | 0.44    |
| CACS change                                | 10.5 ± 11.62     | 11.22 ± 7.07      | 13.46 ± 20.12      | 0.86    |
| CACS percentage change, %                 | 89.32 ± 147.81   | 35.45 ± 21.79     | 40.65 ± 46.44      | 0.35    |
| Baseline RI                                | 0.96 ± 0.30      | 1.00 ± 0.35       | 0.96 ± 0.35        | 0.74    |
| Follow-up RI                               | 1.06 ± 0.35      | 1.12 ± 0.32       | 0.97 ± 0.32        | 0.10    |

Values are expressed as the mean ± SD or % (n).

1 The total number of plaques includes only non-calcified plaques and mixed plaques.

2 Coronary artery calcification score (CACS) assessment includes 38 patients with CACS in the study population (Group I, n = 18; Group II, n = 9; Group III, n = 11). CACS: Coronary artery calcification score; RI: Remodelling index.

### ARTICLE HIGHLIGHTS

#### Research background
The cardiovascular benefit of statins depends on their compliance, and the cardiovascular events may be related to discontinued application of statins. However, it is unclear whether different administration methods have an effect on coronary artery plaques.

#### Research motivation
Taking statins can cause plaque regression, but the effects of discontinued and intermittent statins applications on coronary artery plaques are unclear.

#### Research objectives
To analyse the effects of different statin application methods on plaques in patients.
with coronary atherosclerosis.

**Research methods**

Patients were divided into three groups: Discontinued application of statins, intermittent application of statins, and sustained application of statins groups. The effects of the different statins application methods on coronary atherosclerotic plaques were assessed.

**Research results**

The results found the volume change and rate of change in the most severe plaques significantly decreased and correlated positively with low density lipoprotein cholesterol (LDL-C) only in the sustained statins application group, but there were no changes in the intermittent and discontinued statins application groups.

**Research conclusions**

Only with continuous statin administration can a reduction in LDL-C levels result in plaque volume shrinkage, but not discontinued or intermittent administration of statins.

**Research perspectives**

It is important to strengthen the management of patients and the promotion of patients’ medication compliance and truly improve clinical prognosis.

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