Atorvastatin Leads to Stabilization and Regression of Coronary Plaque Trials -Evaluation With Simultaneous Angioscopic and Intravascular Ultrasound Examination- (TWINS STUDY)

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Osaka Police Hospital, Osaka

Division of Cardiology, Nihon University School of Medicine
**Background**

- Lipid lowering therapy with statins reduces the cardiac events via plaque modification shown by the intravascular ultrasound (IVUS) and angioscopy.
- IVUS examination suggested the regression or prevention of the progression of plaque.
- Angioscopic examination showed the change in plaque color.
- However, there were no studies to reveal the effect of statins on plaque modification using both IVUS and angioscopy.
Background (continued)

- IVUS can measure the plaque volume to evaluate the progression or regression.
- Coronary angioscopic observation revealed that plaque with the increased yellow color became more vulnerable, then ruptured. So, coronary angioscopy can assess the plaque surface to evaluate the stability.
Objectives

To study the serial changes in coronary plaques by using IVUS and coronary angioscopy, then reveal the mechanism of the reduction of cardiac events by statins.
# Study organization

## Principal Investigator

**Kazuhisa Kodama**
Cardiovascular Division, Osaka Police Hospital

## Study Center

- **Osaka Police Hospital** (Atsushi Hirayama, Yasunori Ueda)
- **Division of Cardiovascular Medicine Department of Medicine, Nihon University School of Medicine** (Tadateru Takayama, Junko Honye, Yuxin Li, Satoshi Saitoh)

## Angioscopic Findings Review Board

- **Shinsuke Nanto**
  Cardiovascular division, Kansai Rosai Hospital
- **Osamu Yamaguchi**
  Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine

## IVUS Analysis Review Board

- **Kenji Takazawa**
  Department of Cardiology, Tokyo Medical University Hachioji Medical Center
- **Junji Yajima**
  Department of Internal Medicine, The Cardiovascular Institute Hospital
**Patients’ selection**

**Inclusion criteria**

- Age; 20-75 year olds
- Coronary heart disease
- LDL-cholesterol $\geq 120$ mg/dL within 8 weeks before the initial administration of 10mg of Atorvastatin.
- Coronary artery with at least one yellow plaque with grade 2 or higher grade observed by angioscopy
Patients’ selection

Exclusion criteria (major)

✓ Acute myocardial infarction within 24 hours
✓ Contraindication of statin
✓ Uncontrolled diabetes mellitus (HbA1c ≥ 8.0)
✓ Others
Study Protocol

Duration before treatment (up to 4 weeks)
- Duration of treatment (80 weeks)
  - 2 weeks
  - 78 weeks

LDL-C ≥ 100 mg/dL Atorvastatin 20 mg/day

LDL-C < 100 mg/dL Atorvastatin 10 mg/day

Confirmation of inclusion and exclusion criteria
Obtaining consent
Angioscopic and IVUS examinations
Prescription for the drug
Baseline

Angioscopic and IVUS examinations
Angioscopic and IVUS examinations

80 weeks
28 weeks
Primary efficacy assessment

- Changes in plaque morphology observed by angioscopy (judged by angioscopic finding Review Board)
- Changes in plaque volume and echogenicity by IVUS (judged IVUS Analysis Review Board)
Assessment of angioscopic findings

Grade 0
no yellow

Grade 1
pale yellow plaque

Grade 2
yellow plaque

Grade 3
intensive yellow plaque

Grade 4
Glittering yellow plaque

Grade 5
ruptured plaque

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IVUS analysis

Range 20 mm

Yellow plaque

Angioscopy
Patients and plaques profile

Informed consent obtained from 71 patients

Enrolled: 57 subjects

Dropouts during observation: 14

Dropouts (including due to different study terms): 14 Subjects excluded from efficacy evaluation: 5 (including one dropout)

0-28 weeks: 39 subjects

Dropouts: 10 subjects

0-28-80 weeks: 29 subjects

10 mg continued: 17 subjects
20 mg incremented: 12 subjects

Plaque number

<table>
<thead>
<tr>
<th>0-28-80 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioscopy</td>
</tr>
<tr>
<td>IVUS (volume)</td>
</tr>
</tbody>
</table>
# Patients’ characteristics (n=29)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>59.0 (8.0)</td>
</tr>
<tr>
<td>Sex, n, (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>24 (82.8)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (17.2)</td>
</tr>
<tr>
<td>Angina, n, (%)</td>
<td>11 (37.9)</td>
</tr>
<tr>
<td>Previous myocardial infarction, n, (%)</td>
<td>19 (65.5)</td>
</tr>
<tr>
<td>Asymptomatic myocardial ischemia, n, (%)</td>
<td>2 (6.9)</td>
</tr>
<tr>
<td>Diabetes mellitus, n, (%)</td>
<td>9 (31.0)</td>
</tr>
<tr>
<td>BMI (SD)</td>
<td>24.4 (3.3)</td>
</tr>
</tbody>
</table>
Changes in LDL-cholesterol

Baseline 28 weeks 80 weeks

Mean ± S.D.

n = 29 subjects

mg/dL

146.2

85.7

87.9

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%Changes in lipid profile

<table>
<thead>
<tr>
<th></th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change at 28 weeks from baseline</td>
<td>-28.5%</td>
<td>-40.1%</td>
<td>-27.8%</td>
</tr>
<tr>
<td>Change at 80 weeks from baseline</td>
<td>-27.8%</td>
<td>-38.7%</td>
<td>-18.7%</td>
</tr>
</tbody>
</table>

Mean ± S.D.

n = 29 subjects
Case (angioscopy)

Grade 3
Baseline
Grade 1
LDL-C 21% ↓
28 weeks
Grade 1
LDL-C 30% ↓
80 weeks

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Case (IVUS)

Baseline

28 weeks

80 weeks

58.2mm³ LDL-C 38% ↓

88.2mm³ LDL-C 48% ↓

96.6mm³
Change in Angioscopic Grade

n = 162

<table>
<thead>
<tr>
<th>Grade</th>
<th>Baseline</th>
<th>28 weeks</th>
<th>80 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.5</td>
<td>1.1</td>
<td>1.2</td>
</tr>
<tr>
<td>Median</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
</tbody>
</table>

* : p < 0.001

Wilcoxon matched-pair signed rank-sum test
**% Changes in IVUS parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± S.D.</th>
<th>Change at 28 weeks from baseline</th>
<th>Change at 80 weeks from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel volume</td>
<td></td>
<td>-5.0</td>
<td>-7.4</td>
</tr>
<tr>
<td>Lumen volume</td>
<td></td>
<td>2.2</td>
<td>NS</td>
</tr>
<tr>
<td>Plaque volume</td>
<td></td>
<td>-9.4</td>
<td>-18.9</td>
</tr>
</tbody>
</table>

* : $p < 0.001$
† : $p < 0.001$

Compared with those before administration, paired t-test.
Compared with those 28 weeks, paired t-test.
Changes in cross point of angioscopic grade and plaque volume

- Grade
  - Baseline
  - 28 week
  - 80 week

- % Change in plaque volume
  - 0
  - -5
  - -10
  - 15
  - -20

- % Change in plaque volume
  - 28 week
  - 80 week

- p < 0.001 *
- p < 0.001 **

- 29 subjects
- 162 yellow plaques
- 57 IVUS volume

- * : Paired t-test
- **: Wilcoxon matched-pair signed rank-sum test

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Summary

✓ Lipid-lowering therapy with Atorvastatin achieved a significant reduction in color of yellow plaque up to 28 weeks and then remained up to 80 weeks.

✓ Lipid-lowering therapy with Atorvastatin increased regression of plaque volume with time at 28 weeks and 80 weeks.

✓ Reduction of yellow color intensity of plaque suggesting vascular endothelium stabilization and plaque regression proceeded along different time courses.
Clinical Implication

In a patient with coronary artery disease, lipid-lowering therapy with Atorvastatin initiated in early phase and continued for a long time is necessary for continuous stabilization of the plaque.
Conclusion

Both stabilization and regression of the coronary plaque by the lipid lowering treatment with Atorvastatin results in the reduction of cardiac event.