



HARVARD MEDICAL SCHOOL  
TEACHING HOSPITAL

# Predictors for Lack of Vascular Response to Statin Therapy

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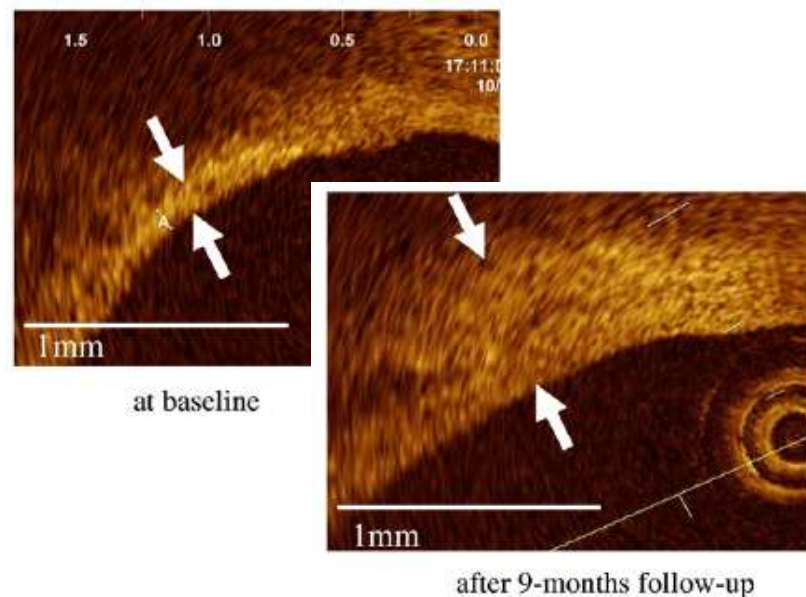
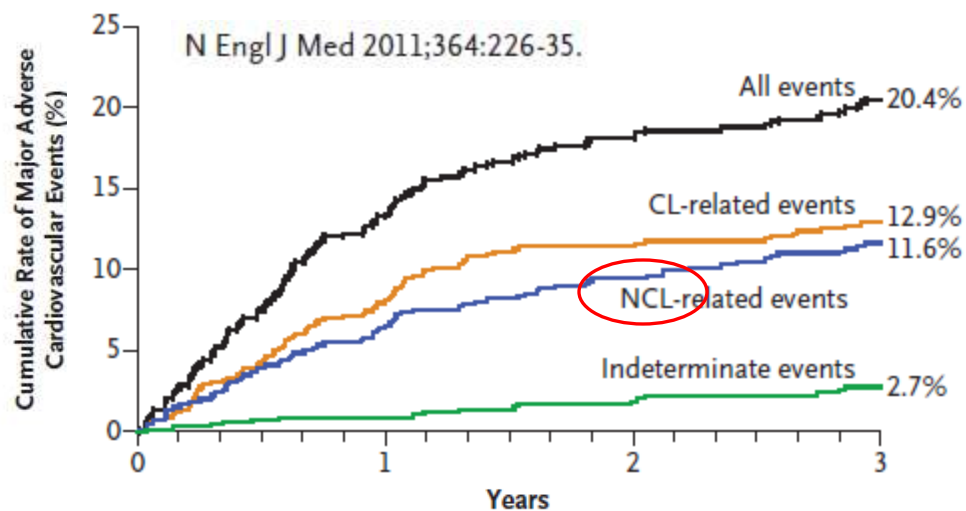
*Michael and Kathryn Park Endowed Chair in Cardiology*



MASSACHUSETTS  
GENERAL HOSPITAL

CORRIGAN MINEHAN  
HEART CENTER

# Background



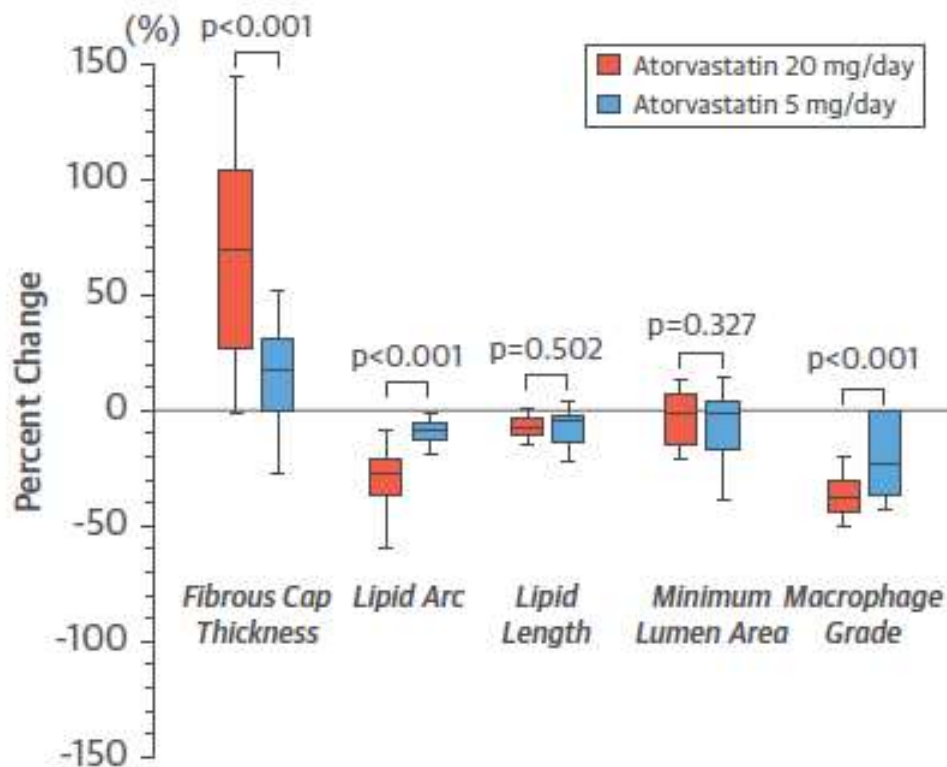
**Table 3. Univariate and Multivariate Logistic Regression Analyses as Predictors of Well-Stabilized Plaques**

|                   | Univariate Analysis<br>OR (95% CI) | p Value | Multivariate Analysis<br>OR (95% CI) | p Value |
|-------------------|------------------------------------|---------|--------------------------------------|---------|
| Age, yrs          | 0.98 (0.93–1.04)                   | 0.60    | —                                    | —       |
| Sex               | 1.6 (0.46–5.4)                     | 0.47    | —                                    | —       |
| Hyperlipidemia    | 0.91 (0.33–2.5)                    | 0.86    | —                                    | —       |
| Hypertension      | 0.43 (0.17–1.1)                    | 0.075   | 0.58 (0.21–1.6)                      | 0.300   |
| Diabetes mellitus | 0.36 (0.14–0.97)                   | 0.042   | 0.68 (0.22–2.1)                      | 0.500   |
| Statin            | 4.6 (1.7–13.0)                     | 0.0033  | 3.5 (1.1–11.0)                       | 0.032   |

The plaques that both the total atheroma volume decreased and the fibrous cap thickness increased were defined as a "well-stabilized plaque."  
CI = confidence interval; OR = odds ratio.

(J Am Coll Cardiol Intv 2010;3:766–72)

# Background



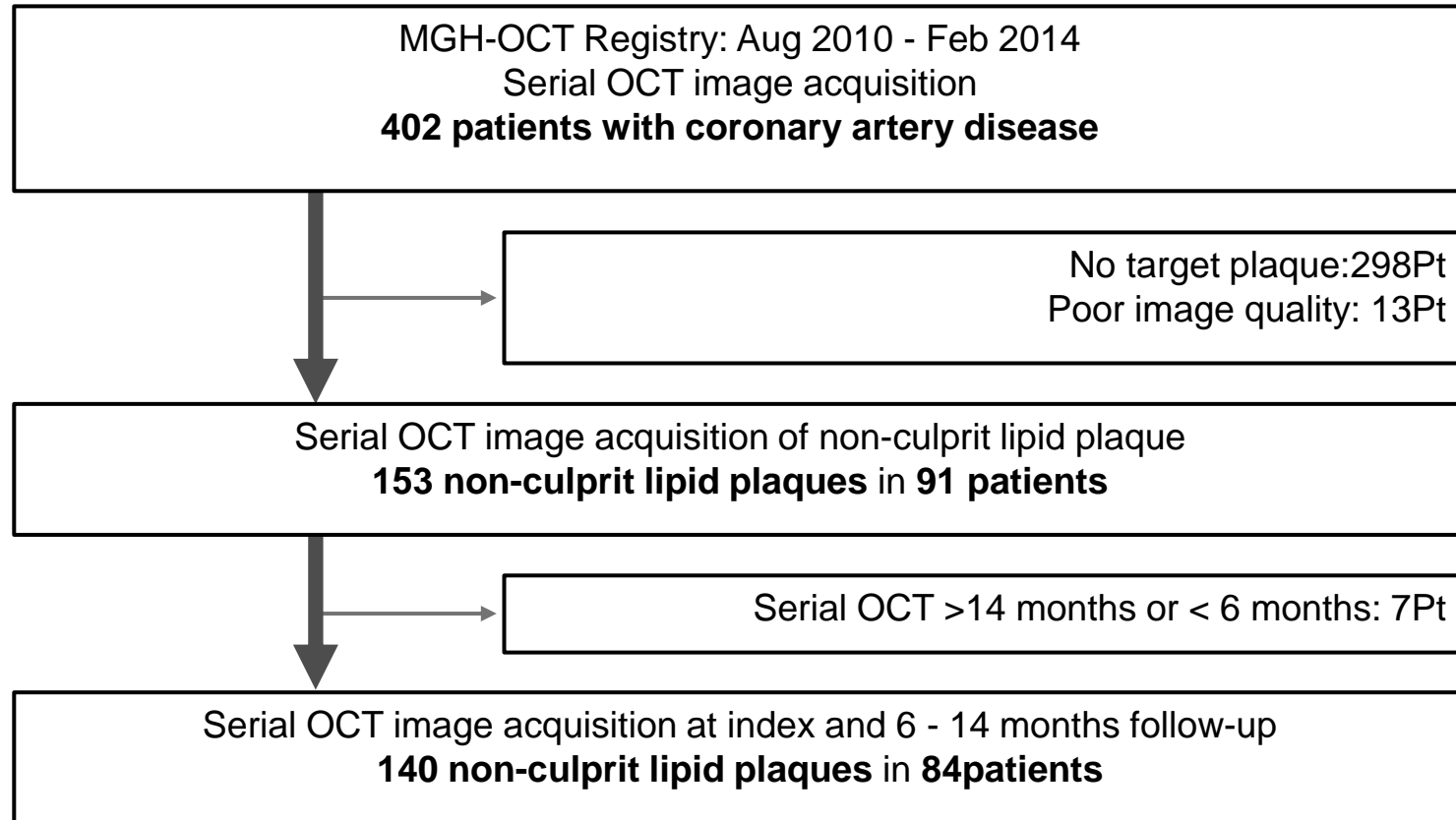
**FIGURE 3** Percentage of Change in Optical Coherence Tomography Measurements Between Baseline and 12-Month Follow-Up

(J Am Coll Cardiol 2014;64:2207-17)

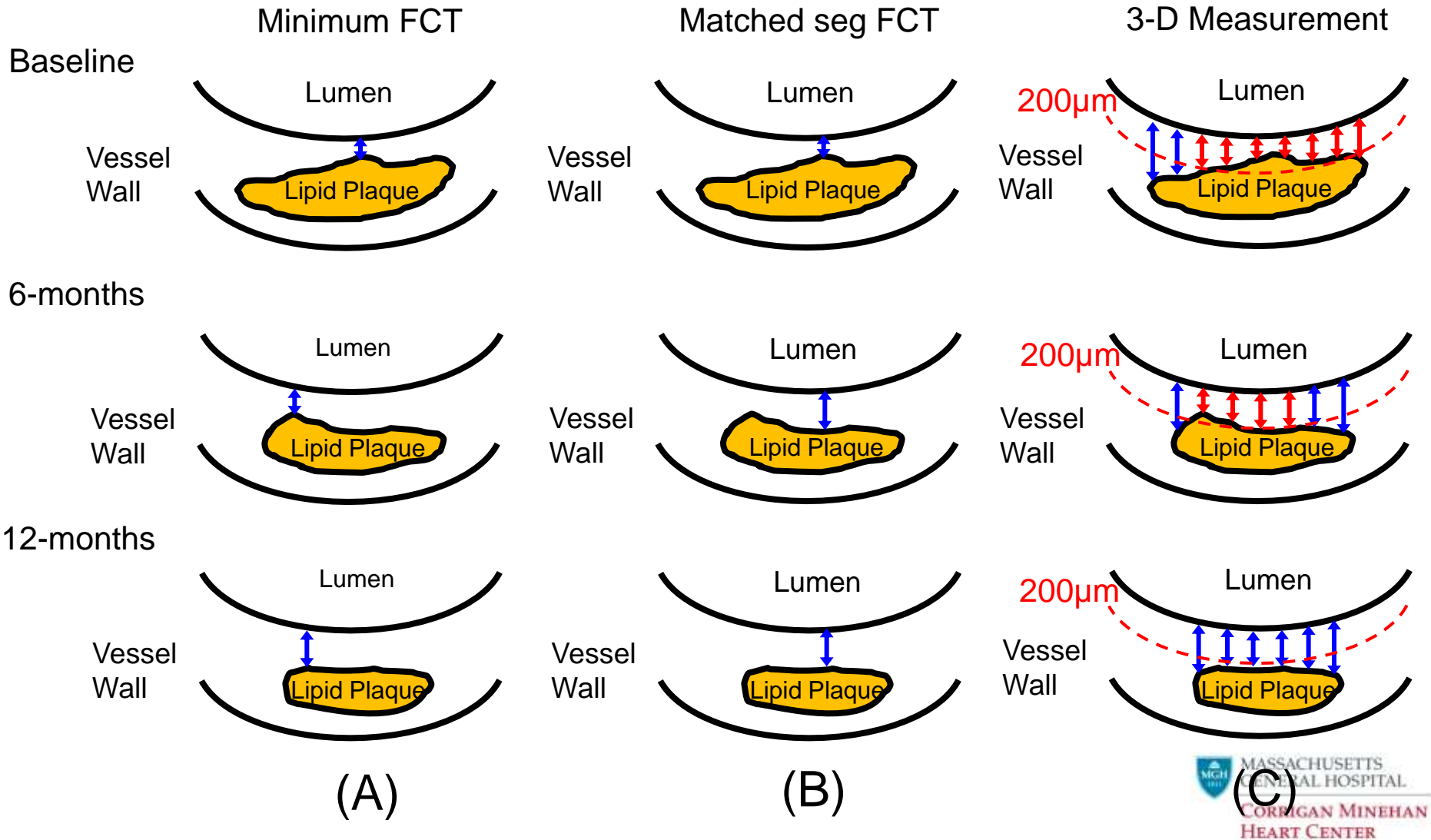
# Aim

To identify clinical predictors for lack of vascular response to statin therapy in patients with CAD.

# Methods

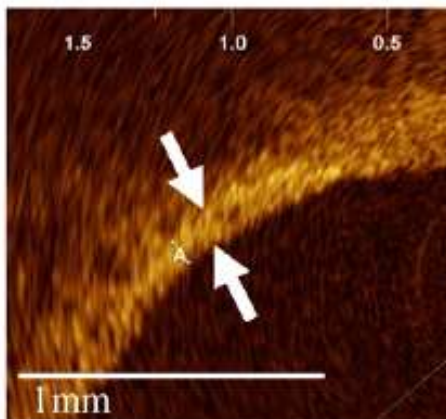


# Fibrous Cap Thickness Measurement

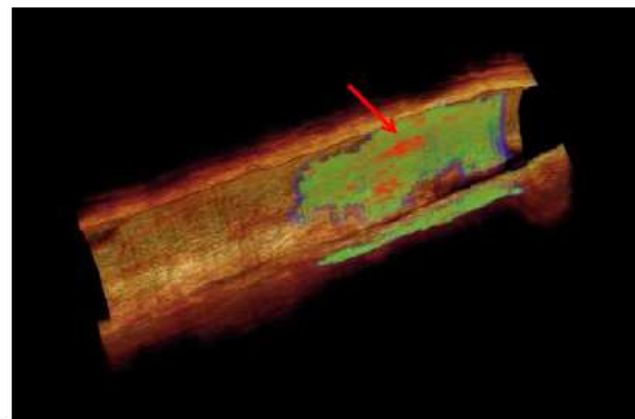
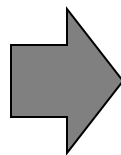


# Methods

## Measurement



Minimum FCT measurement



3D TCFA area measurement

## Study endpoint

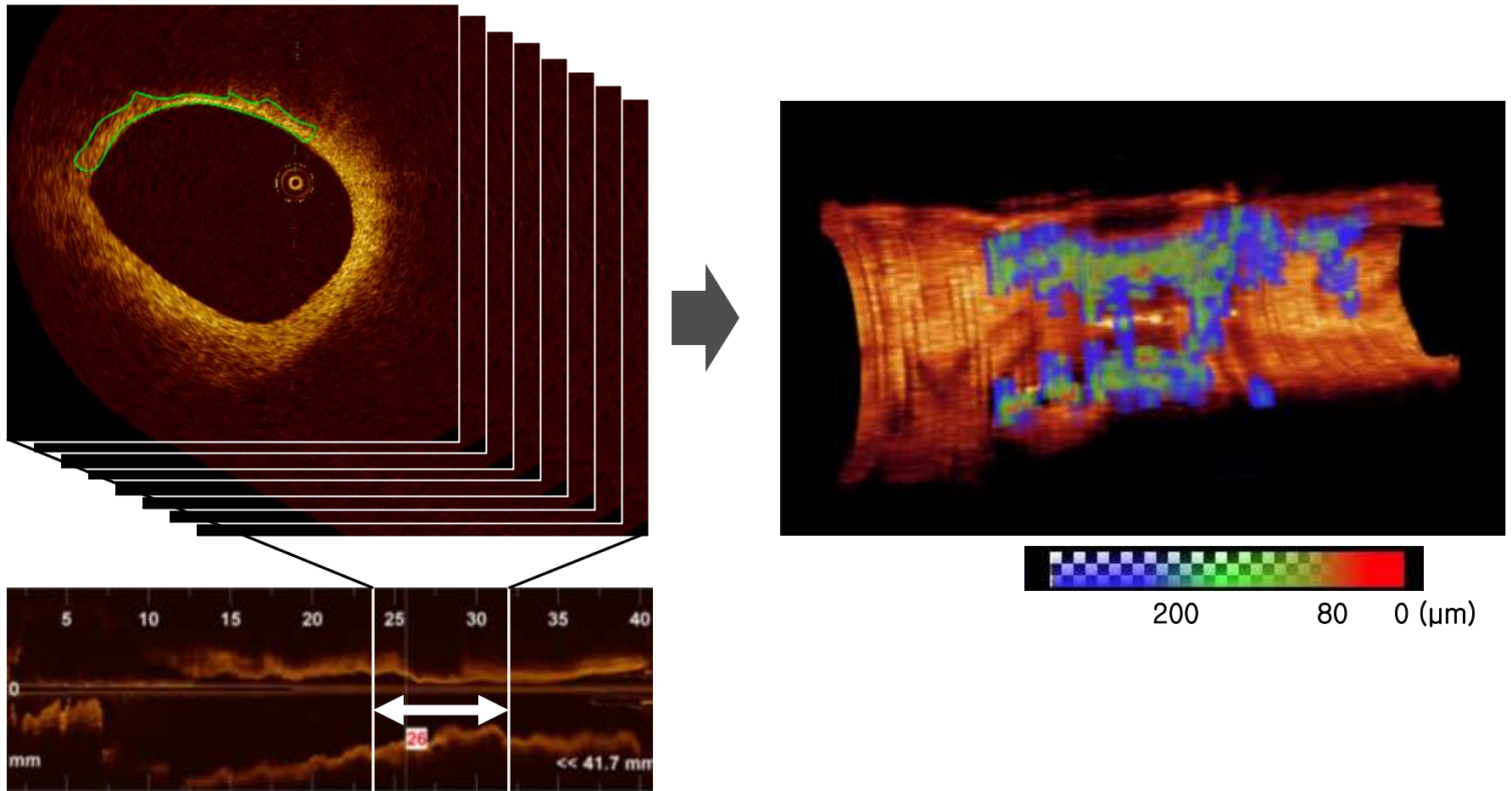
### Primary endpoint

Factors for the change of thin-cap area  $< \underline{200\mu\text{m}^*}$

### Secondary endpoint

Factors for the change of thin-cap area  $< \underline{80\mu\text{m}^*}$

# Methods



Three-dimensional thin-cap area measurement



# Results

# Baseline characteristics

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|                              |                  |
|------------------------------|------------------|
| Follow-up duration, months   | 6.3 [6.1 – 12.1] |
| Age, yrs                     | 59.0 ± 9.9       |
| BMI                          | 24.7 ± 2.4       |
| Male                         | 65 (77.4)        |
| <b>Clinical presentation</b> |                  |
| STEMI                        | 9 (10.7)         |
| NSTEMI-ACS                   | 42 (50.0)        |
| Stable angina                | 33 (39.3)        |
| Previous MI                  | 25 (29.8)        |
| Previous PCI                 | 50 (59.5)        |
| Hypertension                 | 53 (63.1)        |
| Hyperlipidemia               | 68 (81.0)        |
| Diabetes                     | 29 (34.5)        |
| Chronic kidney disease       | 7 (8.3)          |
| Current smoker               | 26 (31.0)        |
| Family history of IHD        | 4 (4.8)          |
| LVEF, %                      | 63.5 ± 8.4       |

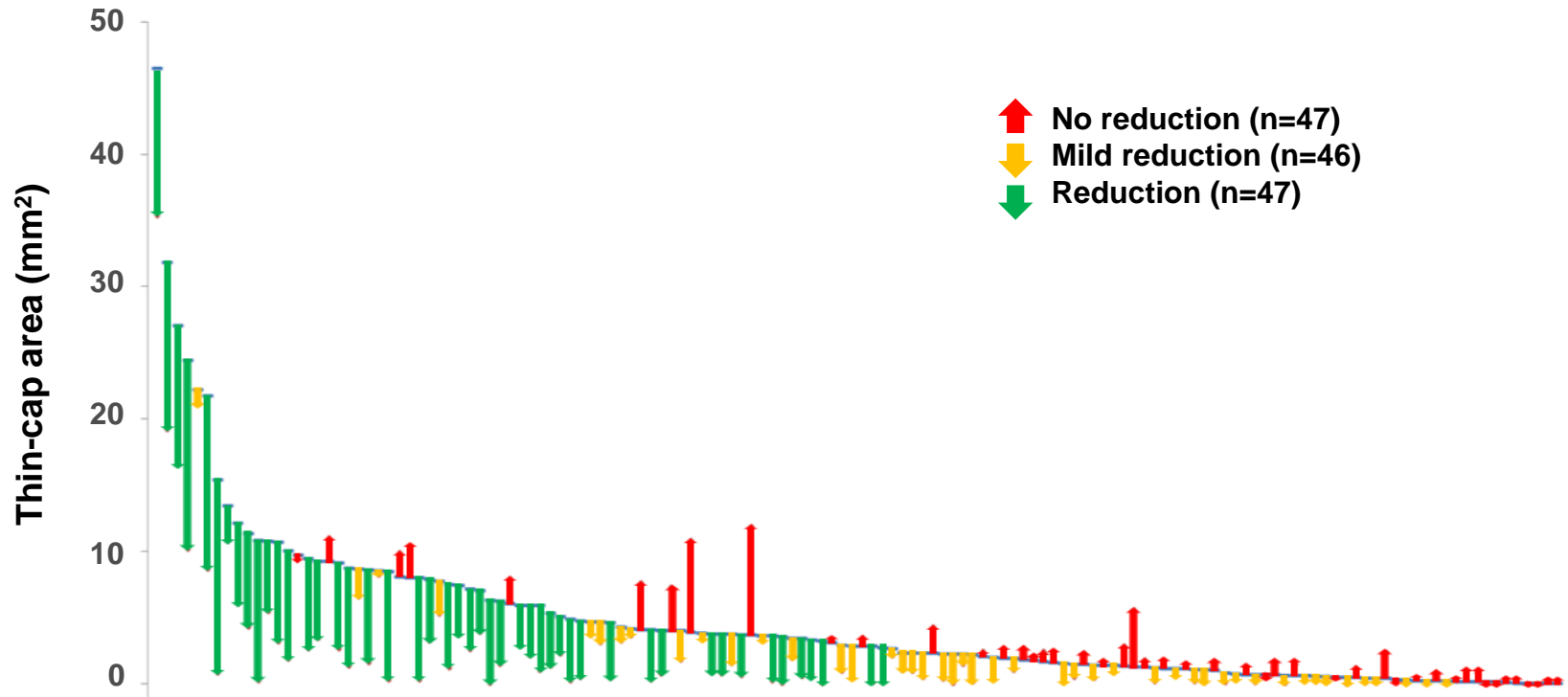
# Laboratory Findings

|                                     | Baseline              | Follow-up            | Change              | P value          |
|-------------------------------------|-----------------------|----------------------|---------------------|------------------|
| Total cholesterol, mg/dl            | 170.6 ± 39.7          | 151.1 ± 34.3         | -19.5 ± 46.2        | <b>&lt;0.001</b> |
| LDL-C, mg/dl                        | 92.9 ± 30.1           | 76.3 ± 23.3          | -16.6 ± 33.6        | <b>&lt;0.001</b> |
| HDL-C, mg/dl                        | 45.0 ± 12.2           | 45.9 ± 13.5          | 0.92 ± 13.6         | 0.545            |
| LDL/HDL ratio                       | 2.18 ± 0.83           | 1.76 ± 0.67          | -0.42 ± 0.83        | <b>&lt;0.001</b> |
| Triglyceride, mg/dl                 | 148.8 [102.7 – 195.7] | 127.5 [88.6 – 168.0] | -15.1 [-66.9, 13.8] | <b>0.007</b>     |
| hsCRP, mg/L                         | 1.0 [1.0 – 3.0]       | 1.0 [0.0 – 2.0]      | -1.0 [-3.0, 0.0]    | <b>0.006</b>     |
| eGFR, ml/min per 1.73m <sup>2</sup> | 83.4 ± 19.2           | 80.8 ± 20.1          | -2.61 ± 16.9        | 0.179            |
| HbA1c, %                            | 6.38 ± 1.34           | 6.18 ± 0.96          | -0.03 ± 0.57        | 0.154            |

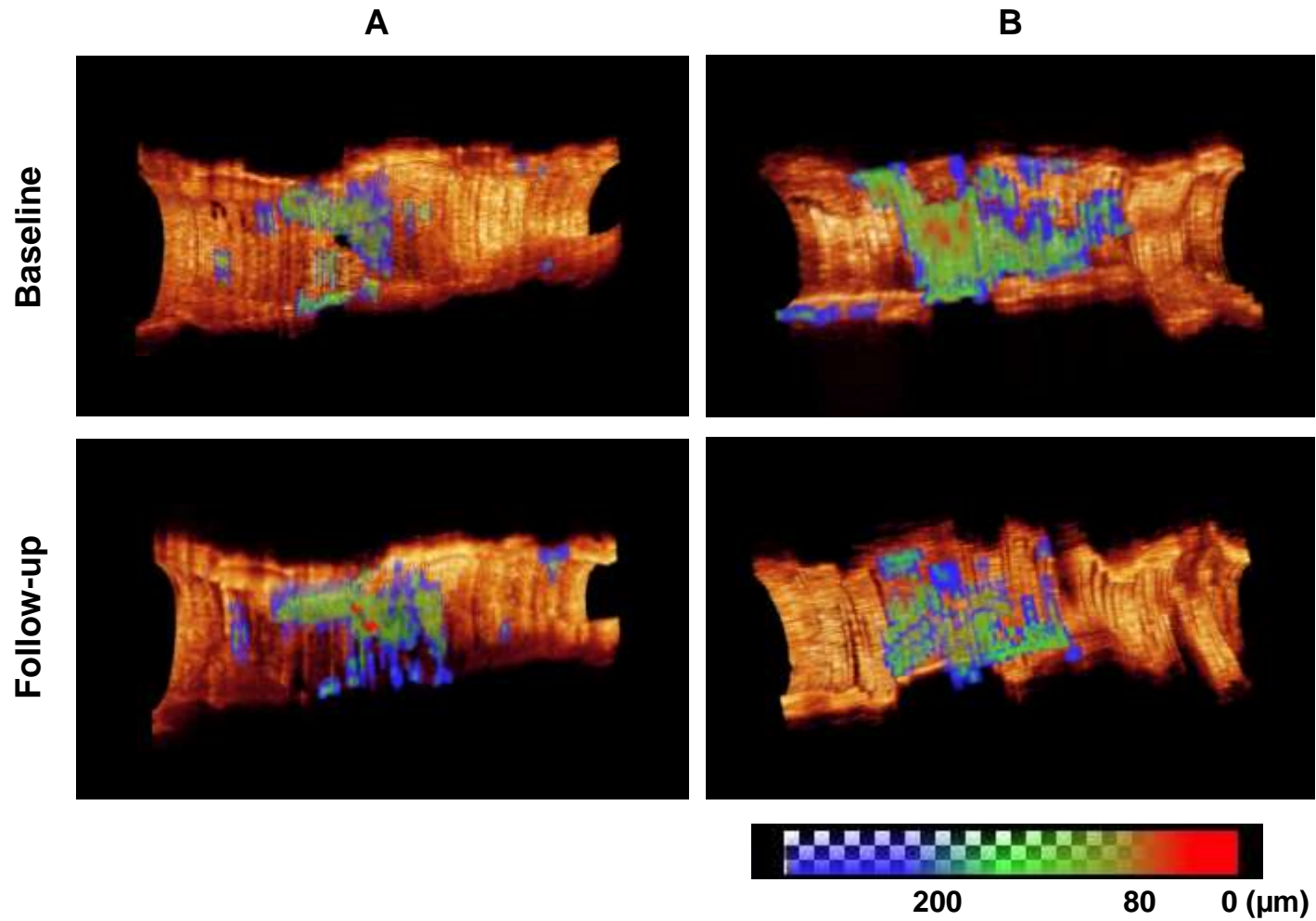
# OCT findings of target plaque:

|                                       | Baseline             | Follow-up            | Change              | P value          |
|---------------------------------------|----------------------|----------------------|---------------------|------------------|
| <b>3D quantitative assessment</b>     |                      |                      |                     |                  |
| Thin-cap area (mm <sup>2</sup> )      | 2.852 [1.023, 6.157] | 1.210 [0.250, 3.192] | -0.94 [-3.25, 0.13] | <b>&lt;0.001</b> |
| <b>2D quantitative assessment</b>     |                      |                      |                     |                  |
| Thinnest fibrous cap thickness (μm)   | 117.2 ± 63.1         | 145.9 ± 66.6         | 28.7 ± 67.3         | <b>&lt;0.001</b> |
| TCFA (<65μm)                          | 35 (25.0)            | 23 (16.4)            | -                   | <b>0.077</b>     |
| Mean lipid arc (°)                    | 164.0 ± 58.3         | 148.5 ± 56.7         | -15.5 ± 49.7        | <b>&lt;0.001</b> |
| Maximum lipid arc (°)                 | 232.1 ± 70.0         | 215.1 ± 76.6         | -17.0 ± 65.1        | <b>0.002</b>     |
| Lipid length (mm)                     | 7.91 ± 3.63          | 7.27 ± 3.99          | -0.64 ± 2.43        | <b>0.002</b>     |
| Lipid volume index                    | 1346.9 ± 835.0       | 1178.6 ± 903.9       | -179.2 ± 644.2      | <b>0.002</b>     |
| Minimal lumen area (mm <sup>2</sup> ) | 3.08 ± 1.29          | 3.05 ± 1.49          | -0.03 ± 1.10        | 0.765            |
| %Area stenosis                        | 59.9 ± 9.1           | 56.3 ± 14.7          | -3.58 ± 13.8        | <b>0.003</b>     |
| Macrophage grade                      | 4.0 [1.0, 9.0]       | 3.0 [0.0, 7.0]       | -1.0 [-4.0, 2.0]    | <b>0.012</b>     |
| <b>Qualitative assessment</b>         |                      |                      |                     |                  |
| Cholesterol crystal                   | 24 (17.1)            | 16 (11.4)            | -                   | 0.17             |
| Microchannel                          | 42 (30.0)            | 42 (30.0)            | -                   | 1.00             |
| Calcium                               | 74 (52.9)            | 73 (52.1)            | -                   | 0.91             |
| Spotty calcium                        | 63 (45.0)            | 65 (46.4)            | -                   | 0.81             |
| Thrombus                              | 4 (2.9)              | 4 (2.9)              | -                   | 1.00             |

# Absolute change of FCT area



# Results



# Absolute change in FCT

|                           | Univariate analysis |                |                  | Multivariate analysis |                |                  |
|---------------------------|---------------------|----------------|------------------|-----------------------|----------------|------------------|
|                           | B                   | 95% CI         | P value          | B                     | 95% CI         | P value          |
| Baseline thin-cap area    | -0.400              | -0.505, -0.295 | <b>&lt;0.001</b> | -0.368                | -0.478, -0.259 | <b>&lt;0.001</b> |
| Follow-up duration, month | -0.307              | -0.527, -0.088 | <b>0.006</b>     | 0.046                 | -0.107, 0.198  | 0.558            |
| Age, yrs                  | 0.089               | 0.033, 0.145   | <b>0.002</b>     | 0.030                 | -0.021, 0.080  | 0.247            |
| BMI                       | -0.090              | -0.319, 0.139  | 0.441            | -0.023                | -0.187, 0.141  | 0.786            |
| Male                      | -0.835              | -2.099, 0.429  | 0.196            | -0.471                | -1.850, 0.908  | 0.503            |
| Acute coronary syndrome   | -2.115              | -3.280, -0.950 | <b>&lt;0.001</b> | -1.535                | -2.561, -0.509 | <b>0.003</b>     |
| Hypertension              | -0.778              | -2.097, 0.542  | 0.248            | -0.885                | -1.999, 0.228  | 0.119            |
| Hyperlipidemia            | -1.016              | -2.457, 0.425  | 0.167            | -0.662                | -1.845, 0.522  | 0.273            |
| Diabetes                  | -0.745              | -2.332, 0.842  | 0.357            | -0.004                | -1.034, 1.025  | 0.993            |
| Current smoker            | -0.963              | -2.422, 0.496  | 0.196            | 0.888                 | -0.388, 2.165  | 0.173            |
| Chronic kidney disease    | 1.293               | -0.344, 2.931  | 0.122            | 1.691                 | 0.350, 3.033   | <b>0.013</b>     |
| Statin naive              | -1.270              | -2.629, 0.089  | <b>0.067</b>     | 0.339                 | -0.778, 1.456  | 0.552            |
| Low-intensity statin      | 2.094               | 1.087, 3.102   | <b>&lt;0.001</b> | 0.930                 | -0.685, 2.545  | 0.259            |
| Beta-blocker              | 0.310               | -1.006, 1.627  | 0.644            | 0.318                 | -0.695, 1.331  | 0.538            |
| ACEI/ARB                  | -0.137              | -1.666, 1.393  | 0.861            | -0.112                | -1.172, 0.949  | 0.836            |

# Clinical Predictors

**Acute coronary syndrome\***

Hypertension

Hyperlipidemia

Male

**Baseline thin-cap area (mm<sup>2</sup>)\***

ACEI / ARB

BMI

Diabetes

Age, yrs

Follow-up duration, month

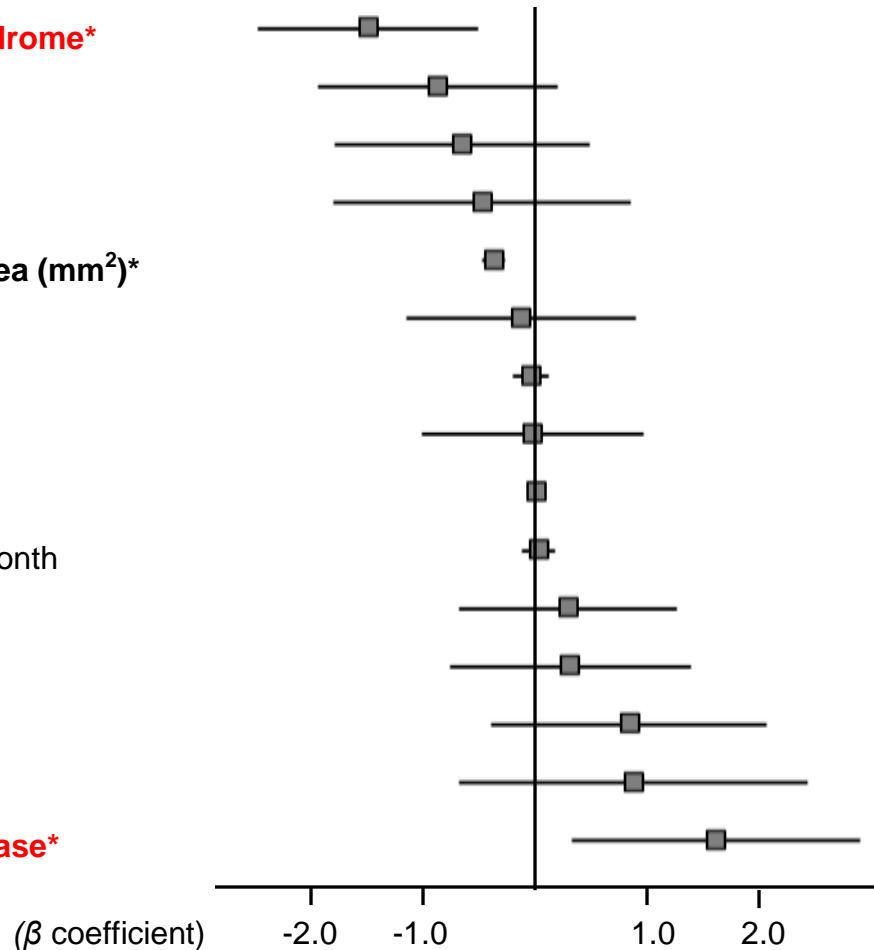
Beta-blocker

Statin naïve

Current smoker

Low-intensity statin

**Chronic kidney disease\***



← Reduction

Thin fibrous  
cap area

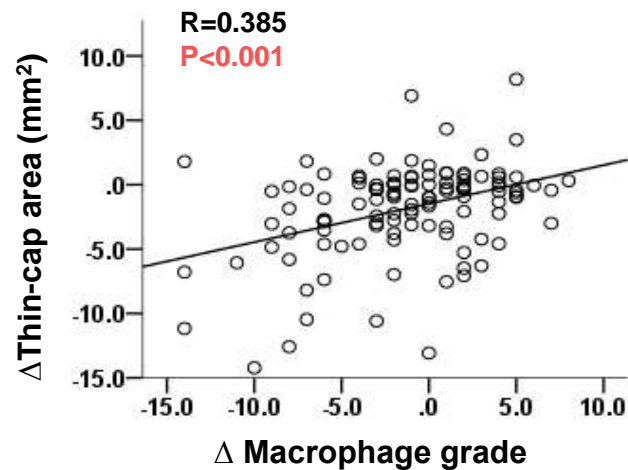
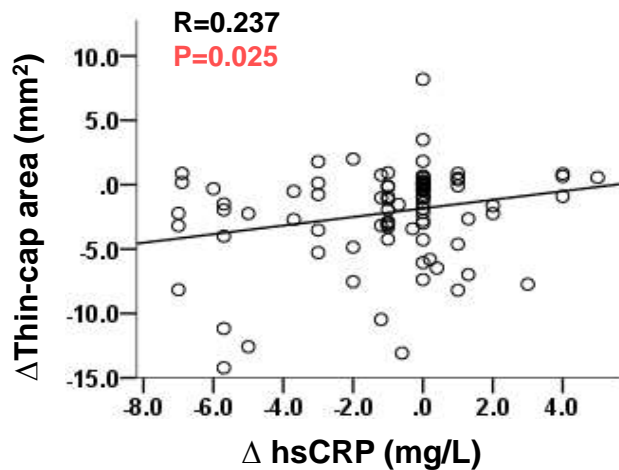
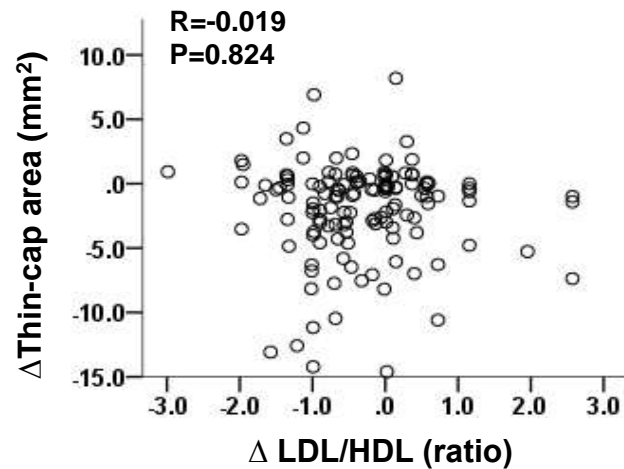
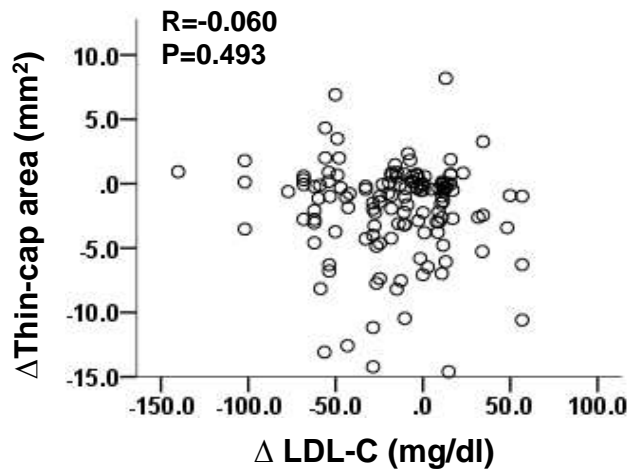
→ Increase



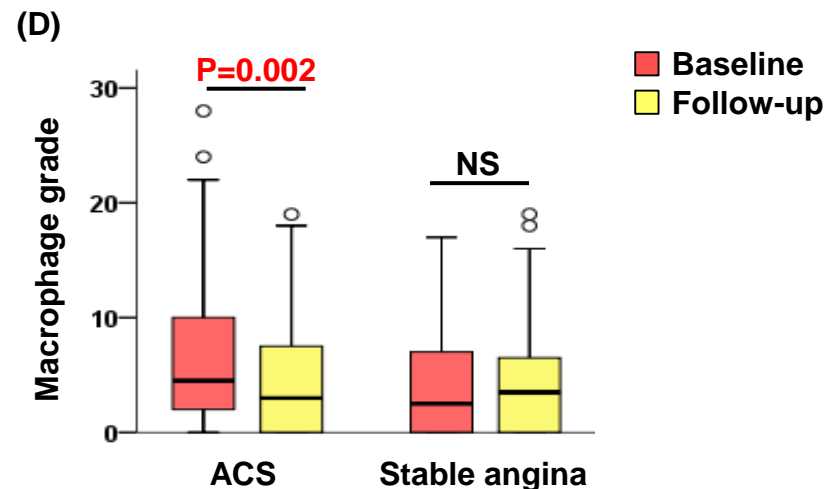
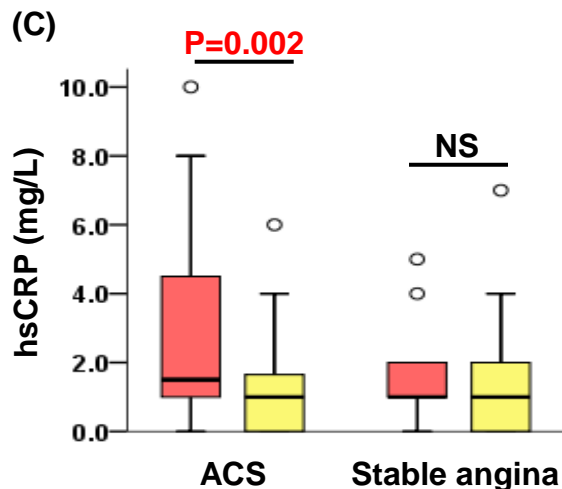
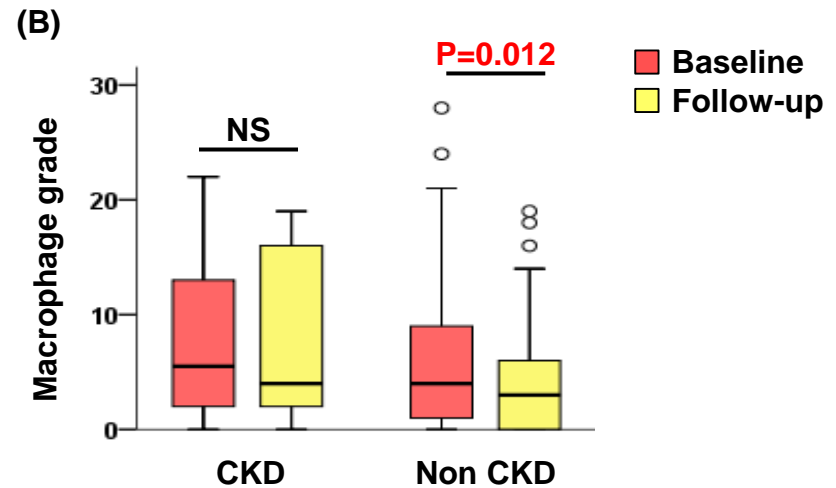
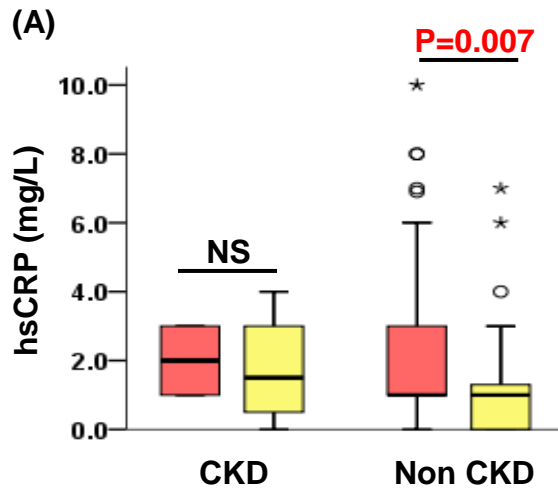
# Thin cap area according to baseline characteristics

|                      | Baseline thin-cap area (mm <sup>2</sup> ) | Follow-up thin-cap area (mm <sup>2</sup> ) | Absolute change (mm <sup>2</sup> ) | P value          |
|----------------------|---|--|------------------------------------|------------------|
| CKD (n=14)           | 2.160 [0.990, 6.453]                      | 1.820 [0.445, 5.771]                       | -0.006 [-2.064, 0.703]             | 0.397            |
| Non CKD (n=126)      | 2.867 [0.959, 6.225]                      | 1.169 [0.223, 3.106]                       | -0.975 [-3.447, 0.057]             | <b>&lt;0.001</b> |
| ACS (n=84)           | 3.613 [1.214, 7.652]                      | 0.951 [0.184, 3.192]                       | -1.950 [-4.605, -0.171]            | <b>&lt;0.001</b> |
| Stable angina (n=56) | 1.927 [0.661, 3.784]                      | 1.502 [0.647, 3.230]                       | -0.297 [-1.617, 0.723]             | 0.271            |

# Correlation between $\Delta$ thin cap area and $\Delta$ lipid/hsCRP



# Change of inflammation status according to baseline clinical presentation



# Summary

- 1) Overall, thin-cap area of non-culprit coronary plaques significantly decreased with statin therapy at 6.3 month F/U.
- 2) CKD was identified as the independent predictor for lack of favorable vascular response to statin therapy.
- 3) ACS was an independent predictor for favorable vascular response to statin therapy.
- 4) The improvement of both systemic and local inflammation status was correlated with the improvement of thin-cap area.

# Conclusion

- CKD is an independent predictor for lack of favorable vascular response to statin therapy.
- ACS is an independent predictor for favorable vascular response to statin therapy.