

Role of lipid-lowering therapy

*Aggressive lipid-lowering therapy with
“atorvastatin and probucol”*

for coronary atherosclerosis determined by 3D-IVUS

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Background

Glistening yellow



Main findings of the current studies

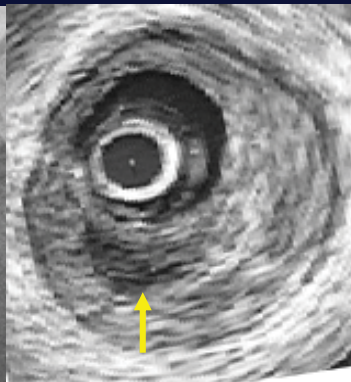
- 1) Asakura et al. used angioscopy to show that yellow plaque, indicating potentially vulnerable plaque, was observed with equal frequency in infarct-related and non-infarct-related arteries.*
- 2) Plaque ruptures occur not only in patients with MI or unstable angina, but are also found in patients with stable angina or no symptoms.*
- 3) Multiple ruptures were seen in 15% of patients in the current population.*
- 4) Ruptured plaques are usually eccentric with positive remodeling.*

*G.Rioufol et al. Circulation. 2002; 106:804, Moriuchi M, Saito S, et al. Heart and Vessels, 1997
A.Maehara et al. JACC. 2002;40:904, JACC 2002;40:904, JACC 2001, 37:1284*

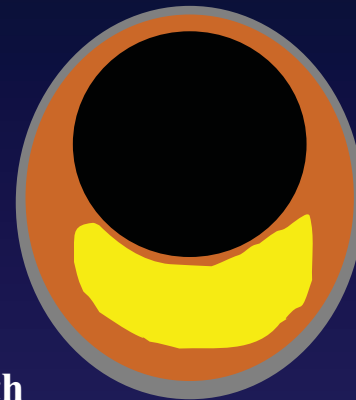
Background

Such lesions frequently appear as non-significant or mild to moderate stenosis on coronary angiography.

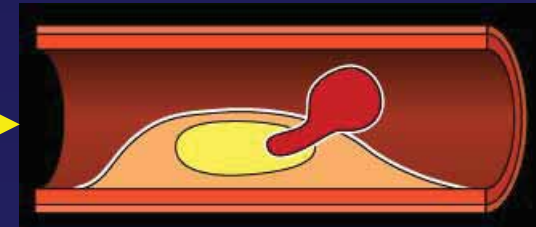
Plaque rupture of the lesion leads to acute coronary syndrome.



Eccentric soft lesion with **lipid pool** and positive remodeling



Angiographically non-significant Stenosis



Background

Therefore, it has been emphasized that treatment to achieve lesion stability and/or regression is beneficial.

Large primary and secondary prevention trials with Statin have demonstrated that lipid-lowering therapy was effective or preventing cardiac events.

Background

Recent studies show that

- 1) Aggressive LDL-C lowering with HMG-CoA reductase inhibition, **atorvastatin**, likely leads to a slowdown of plaque growth and a change in plaque composition. (GAIN)*
- 2) **Reversal study***
- 3) **Probucol** has been reported to prevent atherogenesis by acting as an anti-oxidant and suppressing the oxidative modification of LDL-C and **Probucol** could stabilize plaque.*

M. Scharf et al. Circulation; 104:387

Y. Sasayama et al. JACC; 39:610

REVERSAL

*The **REVERS**ing **A**therosclerosis with **A**ggressive
Lipid **L**owering Study*

Nissen SE et al. JAMA 2004 291:1071-80

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REVERSAL trial

1. **654 patients enrolled and 502 had evaluated by IVUS at baseline and 18mo follow up after lipid lowering therapy with Pravastatin 40mg or Atorvastatin 80mg for the patients with coronary artery disease.**
- **Volumetric IVUS analysis was performed for plaque volume.**

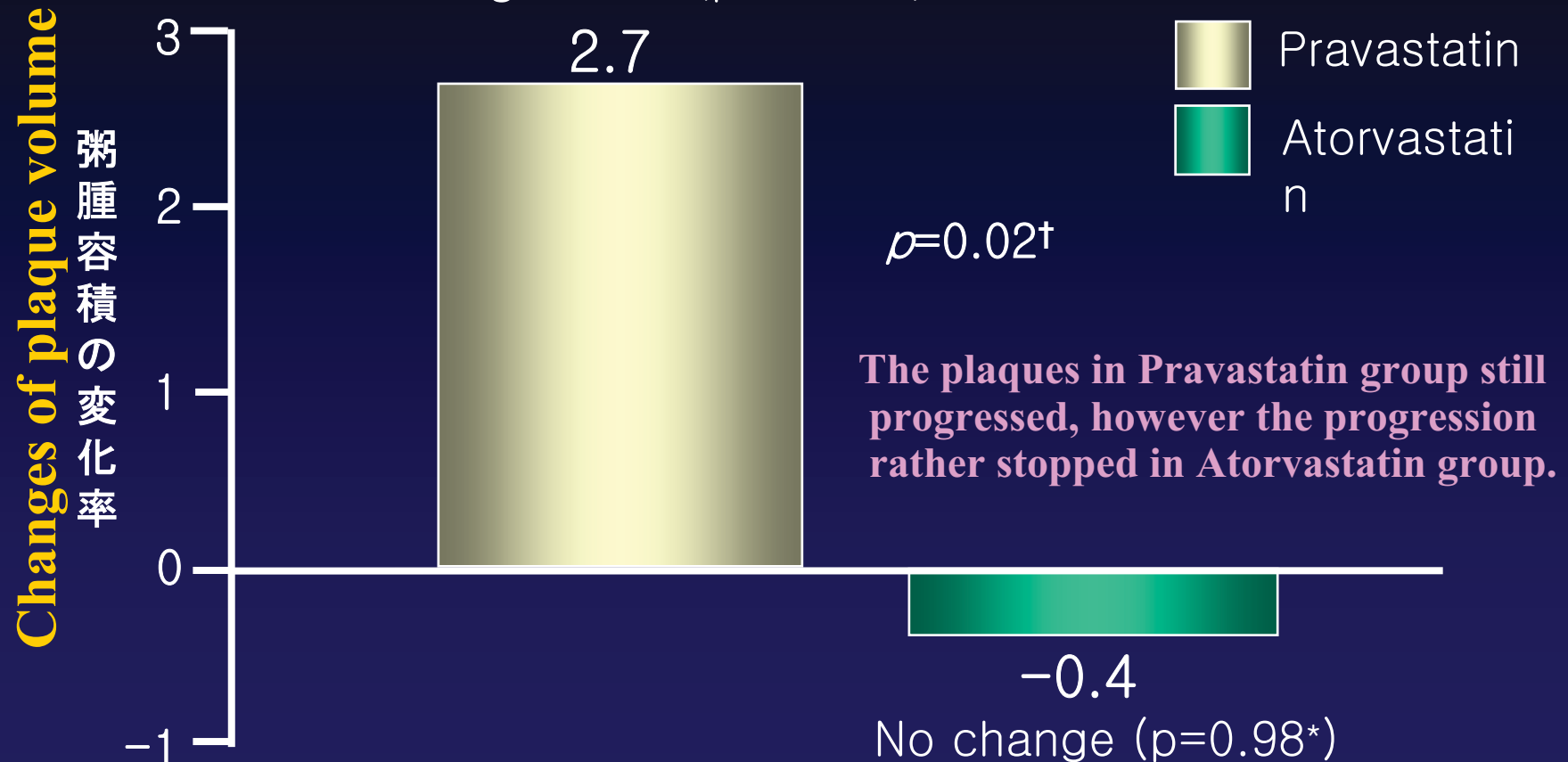
Nissen SE et al. JAMA 2004 291:1071-80

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Changes of Plaque volume

粥腫容積の変化率(一次エンドポイント)

Progression ($p=0.001^*$)



* Wilcon signed rank test

† Wilcon rank sum test

Nissen SE et al. JAMA 2004 291:1071-80

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Therapeutic Strategy of ACS

Aggressive LDL-C lowering

Suppressing the oxidative modification of LDL-C

Purpose

To evaluate the combined effects of aggressive LDL-C lowering therapy with atorvastatin and anti-oxidant therapy with probucol on changes in plaque volume and echogenicity by intravascular ultrasound (IVUS).

Methods: Patients

1. 65 non-culprit lesions in patients with ACS
2. Mild to moderate lesion (< 50% on QCA)
3. Baseline and follow-up studies (> 6 months) with CAG and IVUS (volumetric and densitometric analysis)
4. 3 groups according to LDL-C level:

Group A (Atorvastatin): LDL-C \geq 140 mg/dl

Group P (Probucol): LDL-C < 140 mg/dl

Group A+P: LDL-C \geq 140 mg/dl

Methods: Study Design

Medication:

Group A: atorvastatin 10mg/day

Group P: probucol 500mg/day

**Group A+P: atorvastatin 10mg/day
and probucol 500mg/day**

IVUS analysis

- 1. 40MHz Atrantis (Boston Scientific Scimed Inc.)**
- 2. Using an automatic motor drive unit and pull-back speed at 0.5mm/sec**
- 3. Off-line volumetric IVUS analysis**
(Netra IVUS, Scimage)

Lumen volume

Vessel volume

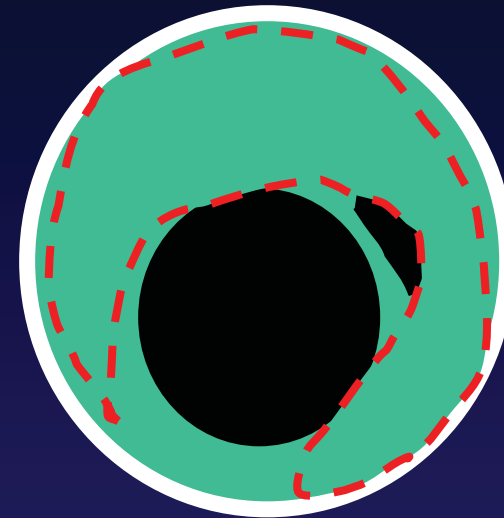
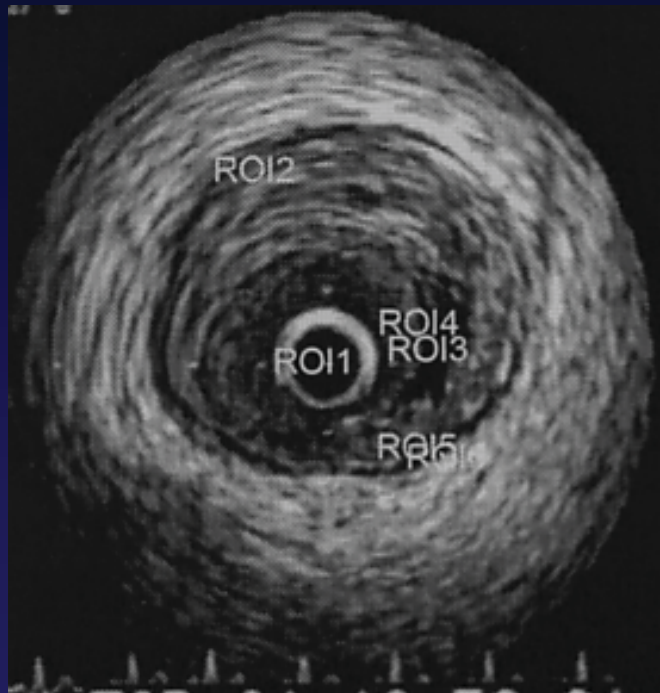
Plaque volume

Texture Videodensitometric Analysis

- 1. Using Contrast Time Analist in Cardio 2000 Win (Fukuda Denshi Co. Ltd.)**
- 2. Contrast Time Investigation analyzes the change of contrast (gray values) in a sequence of IVUS images.**
- 3. Regions of interest (ROI)**
- 4. Gray scales (between black and white, divided into 256 values) for echogenicity.**

Texture Videodensitometric Analysis

Regions of interest (ROI)



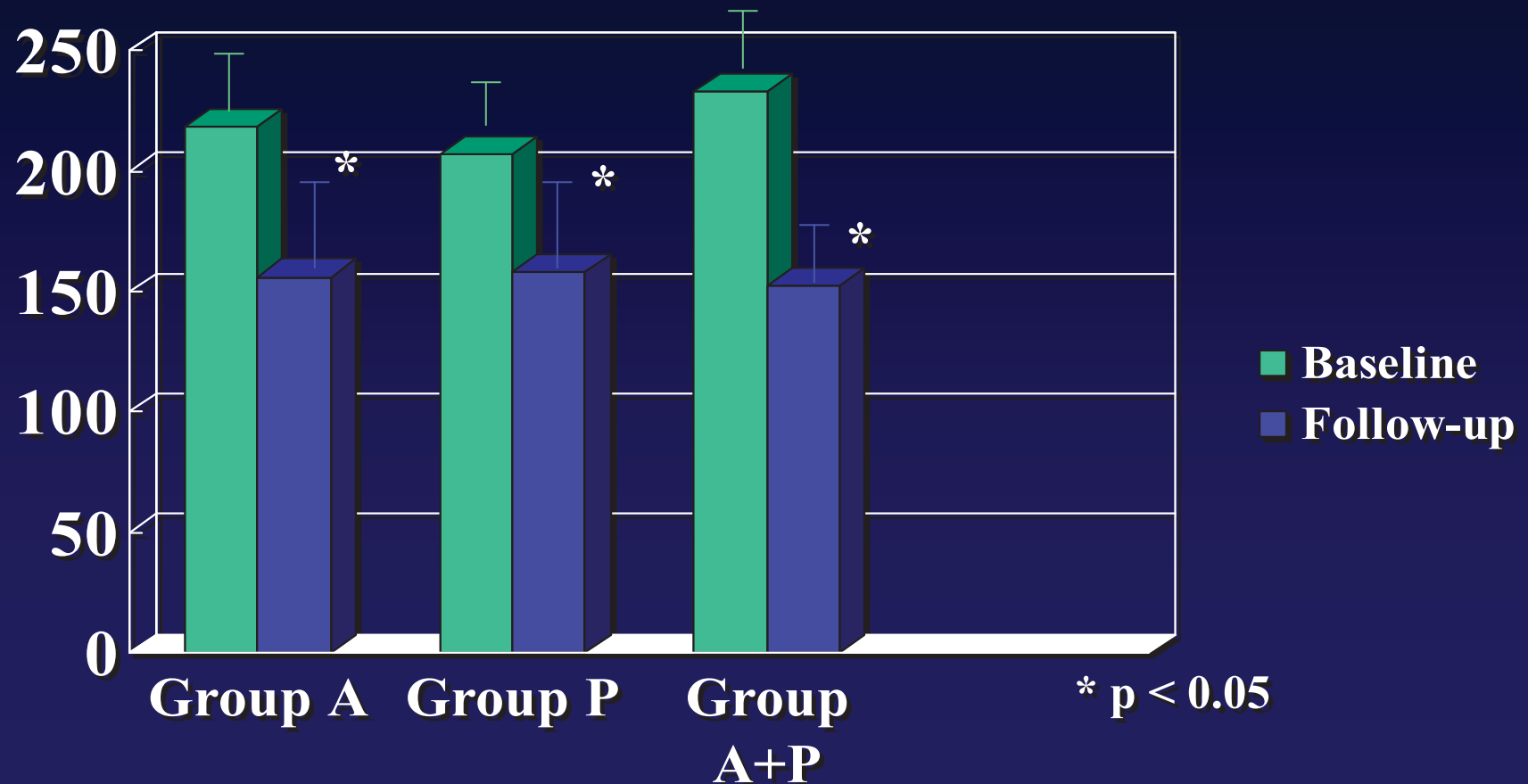
ROI plaque
ROI adventitia

Average gray scale of the lesion for plaque echogenicity.

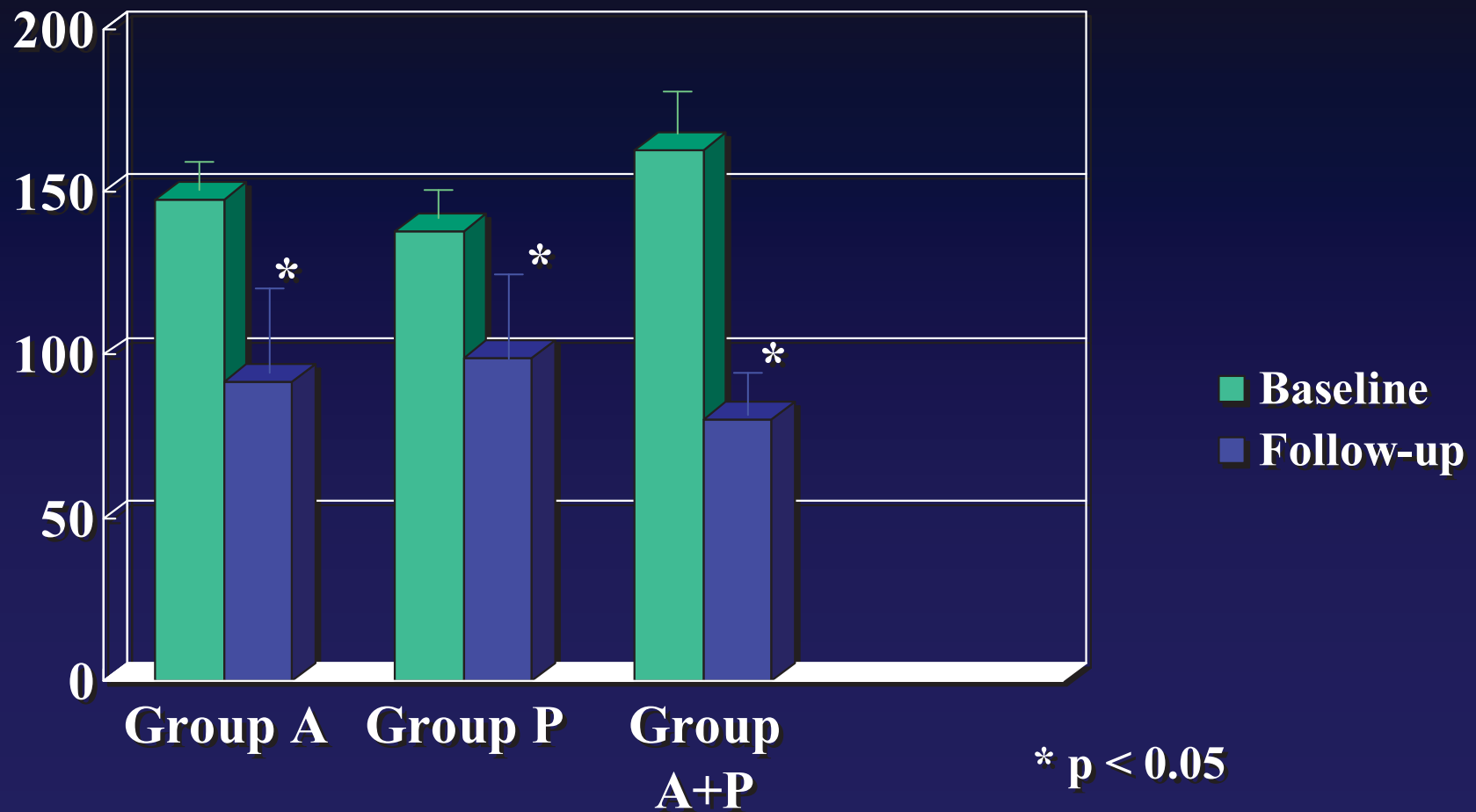
Patient Characteristics

	<u>Group A</u> (n=23)	<u>Group P</u> (n=21)	<u>Group A+P</u> (n=21)
Age (mean)	62.2 ± 12.0	64.4 ± 8.3	57.6 ± 5.2
Follow-up period	6.8 ± 2.1	6.4 ± 1.2	6.4 ± 1.1
Previous MI	5 (50%)	8 (80%)	6 (60%)
LAD	10 (40%)	8 (20%)	7 (30%)
LCX	7 (40%)	6 (20%)	5 (20%)
RCA	6 (20%)	7 (60%)	9 (50%)
Smoking	15 (70%)	14 (80%)	16 (80%)
Hyperlipidemia	15 (70%)	14 (70%)	15 (80%)
Hypertention	14 (70%)	9 (40%)	10 (40%)
Diabetes Mellitus	5 (0%)	7 (40%)	5 (20%)
Family history	4 (20%)	3(10%)	4 (20%)

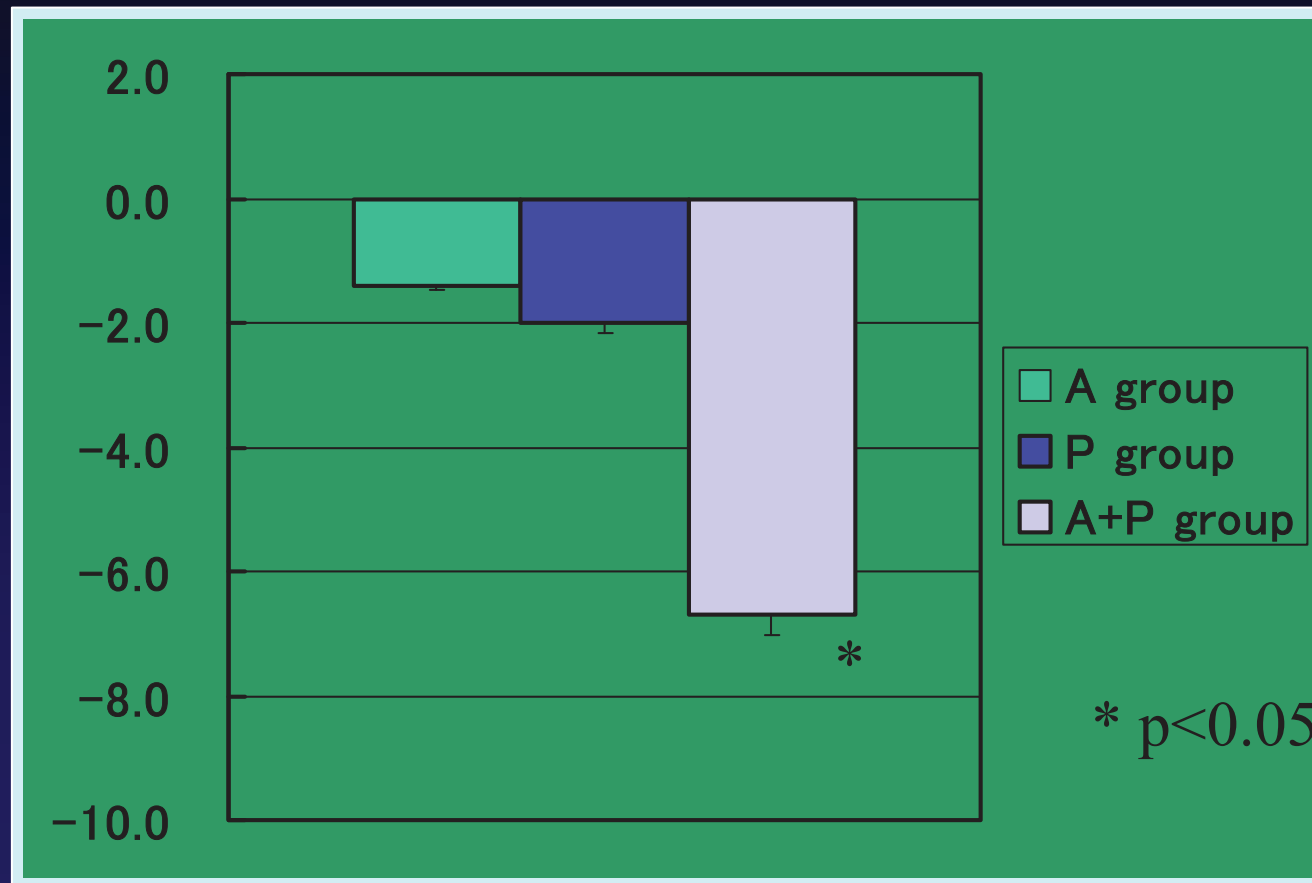
Changes in Total Cholesterol



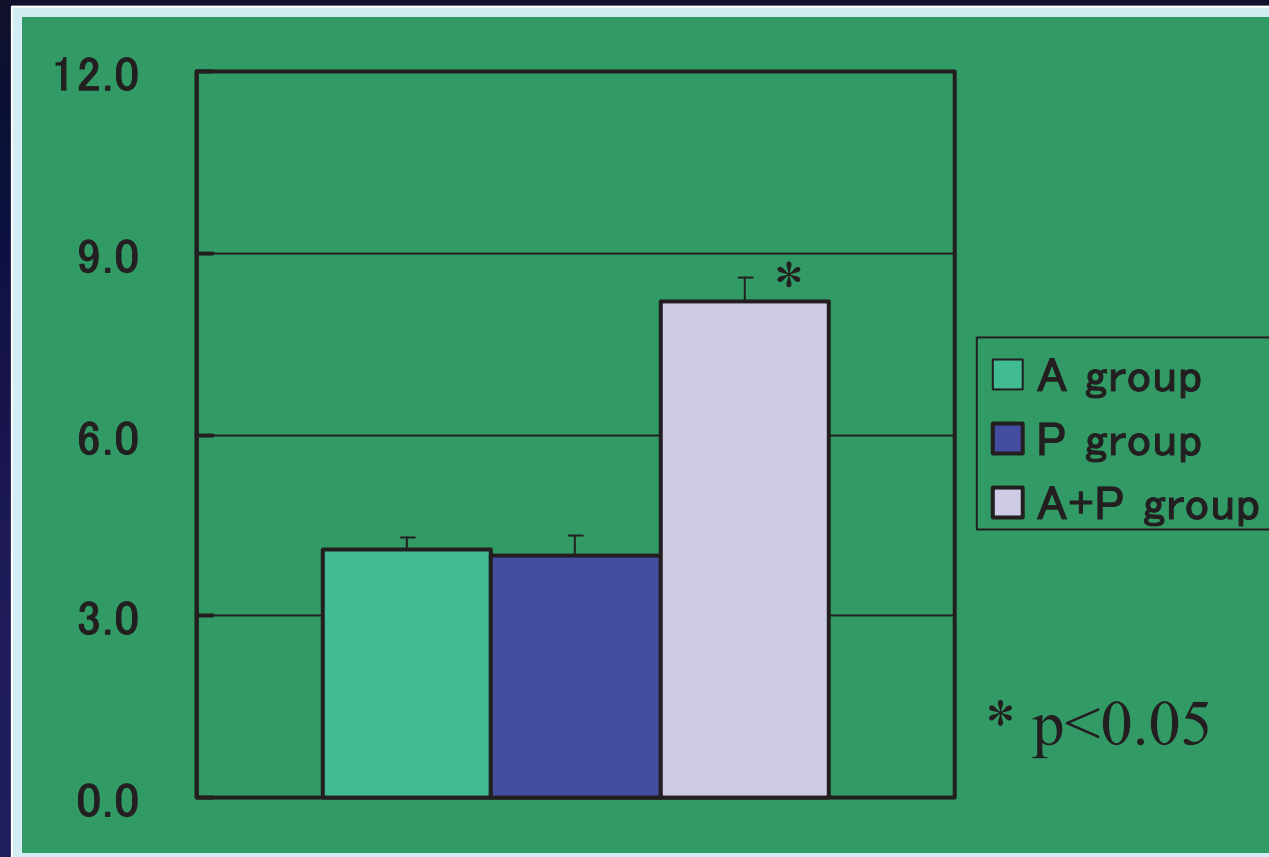
Changes in LDL-C



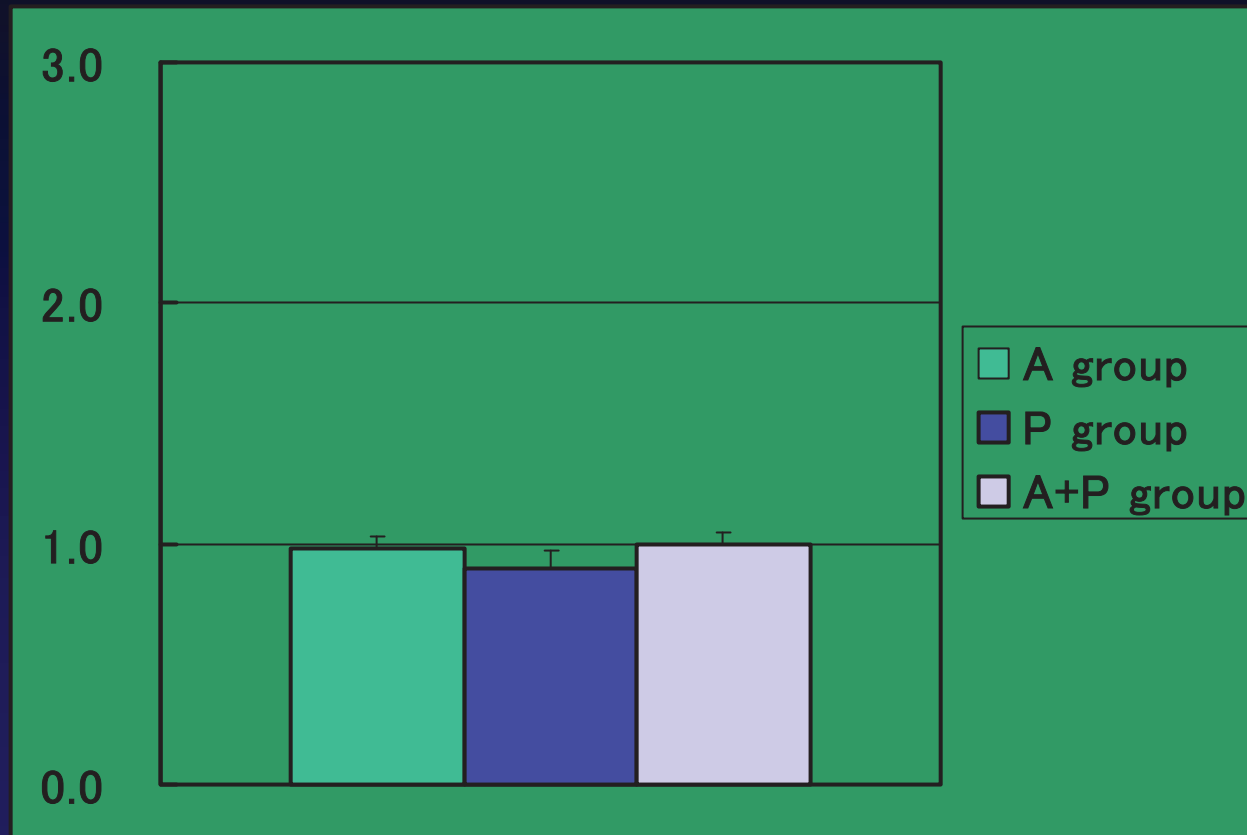
% Change in atheroma volume



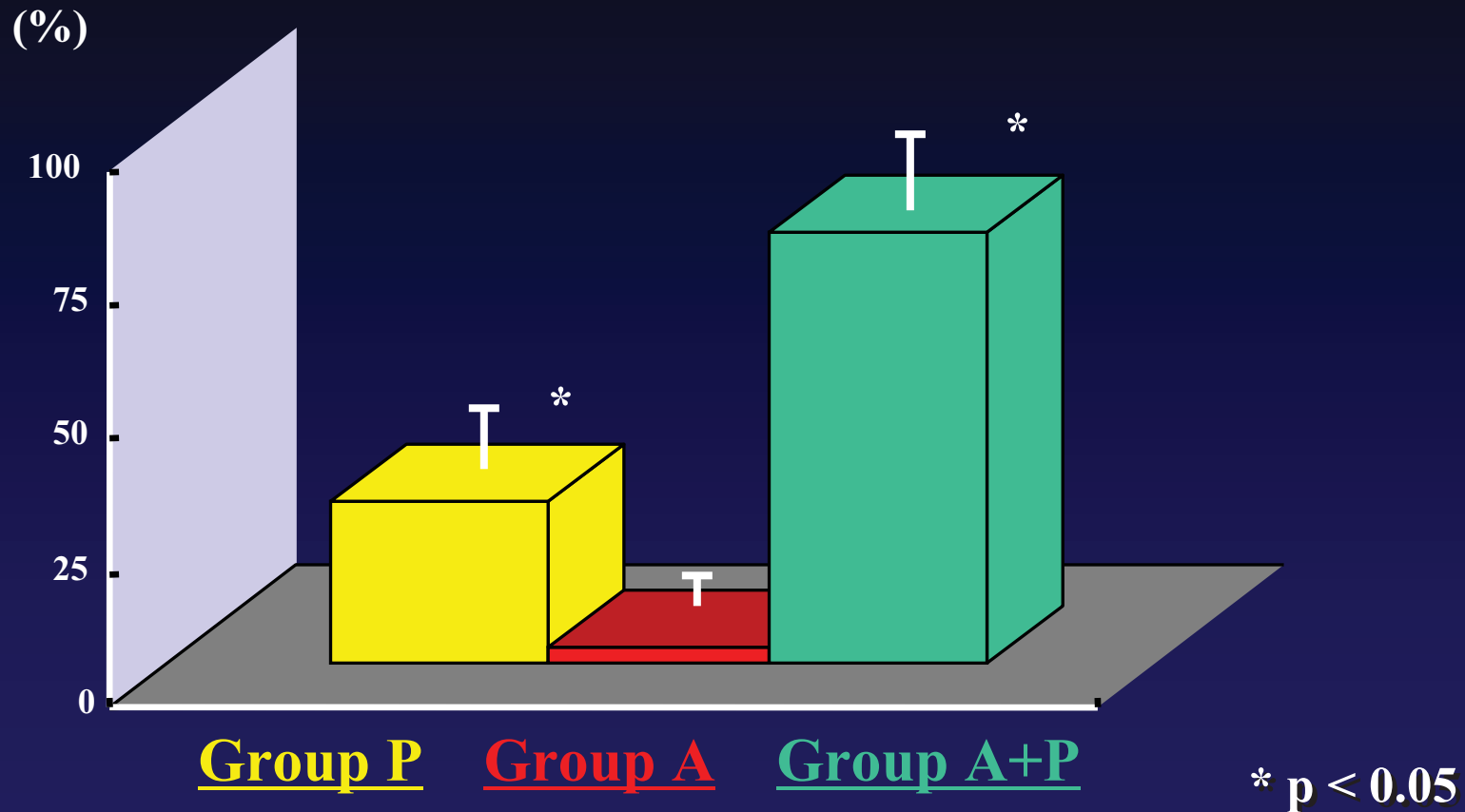
% change in Lumen volume



% changes in vessel volume



% changes in plaque echogenicity



Improvement rate (%) =

$$\frac{(\text{Plaque GV (follow)} - \text{Plaque GV (baseline)})}{\text{Plaque GV (baseline)}} \times 100$$

Coronary angiography



Baseline



Probucol + Atorvastatin

67y/o, Male

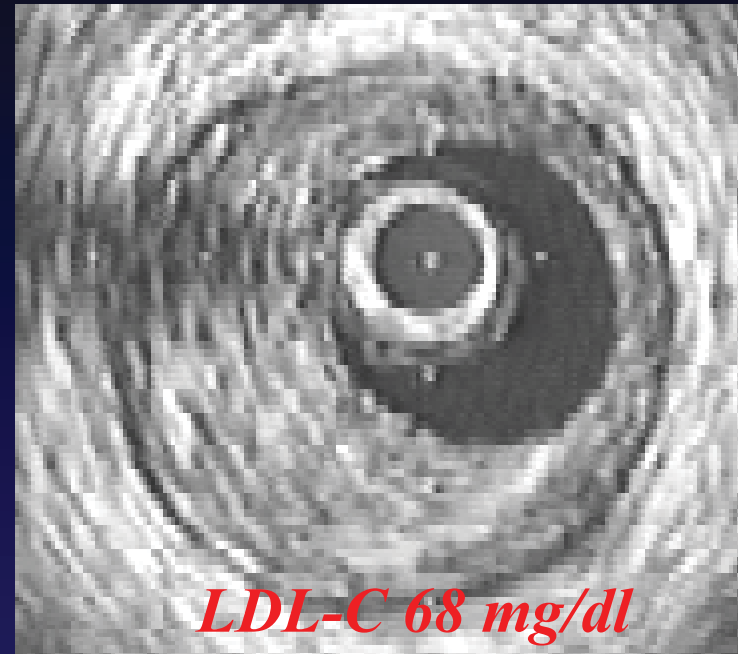
Changes in Plaque Area and Echogenicity

Before treatment



Plaque area: 14.96mm²
Mean gray value: 52.0

Atorvastatin + Probucol



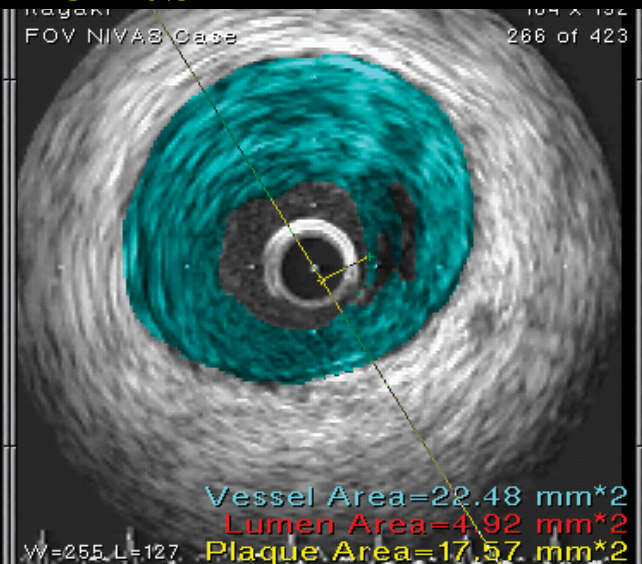
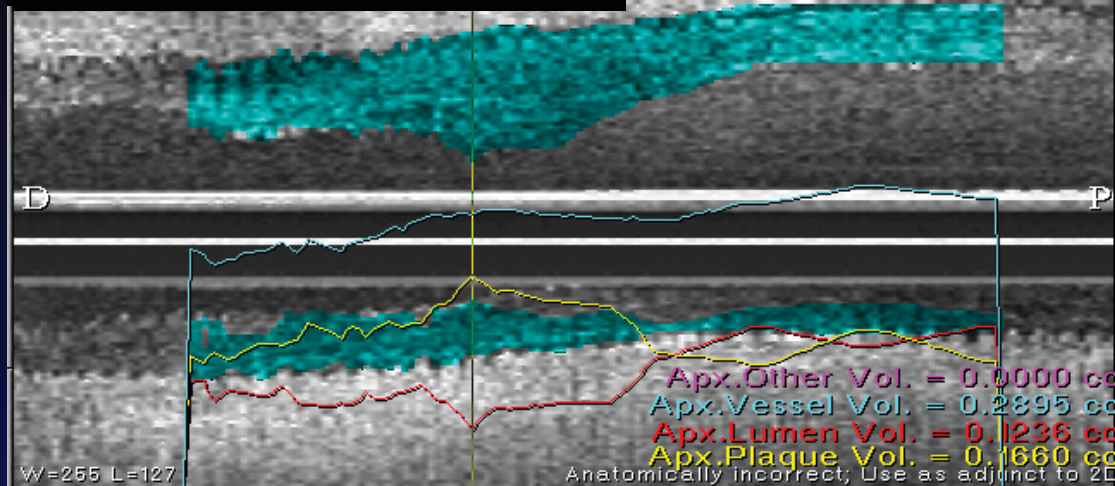
Plaque area: 13.67mm²
Mean gray value: 65.3

M.I., 67y.o. RCA, Male

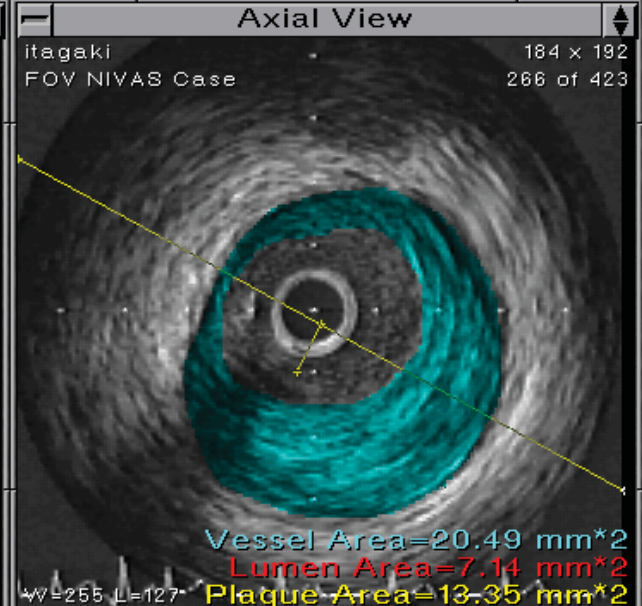
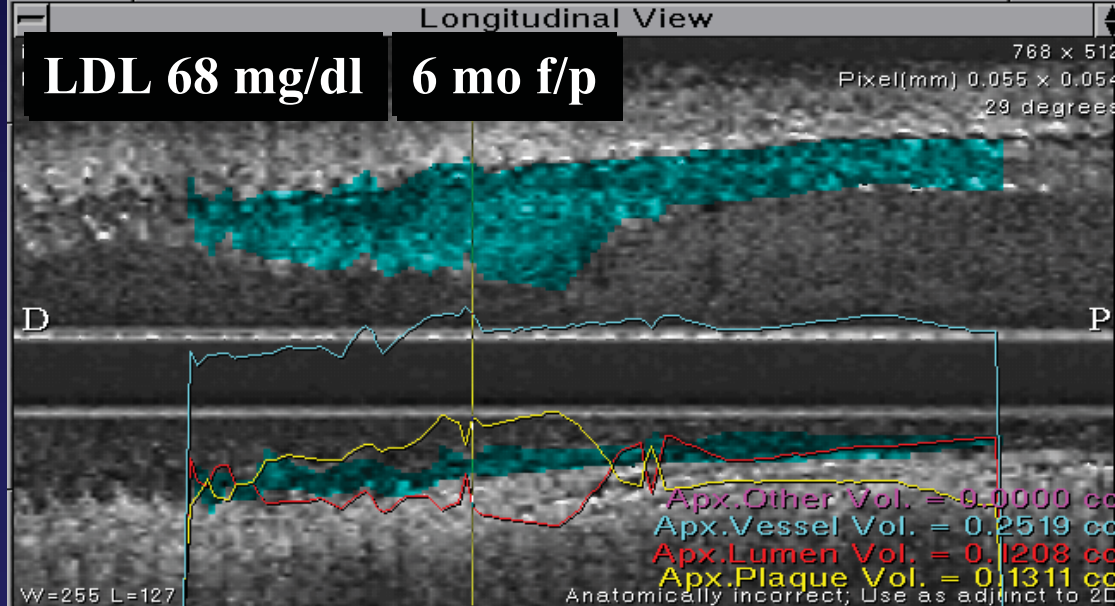
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3D-IVUS measurements

LDL 146 mg/dl Baseline



LDL 68 mg/dl 6 mo f/p



Dual View Image Visualization

Summary

1. Increase in echogenicity on videodensitometric analysis was recognized in all groups, especially in Group A+P > Group P.
2. Significant reduction in plaque volume with concomitant increase in lumen volume was obtained in Group A+P.

Conclusions

1. **LDL-C should be reduced less than 100 mg/dl to slowdown or stop plaque growth.**
2. **Anti-oxidant therapy with probucol might stabilize plaque composition.**
3. **Combination therapy with atorvastatin and probucol may lead to plaque regression and stabilization of minor lesions.**
4. **This therapy could be very useful to prevent cardiac events after PCIs.**
5. **First report of plaque regression!**