대한심장학회 춘계학술대회
Satellite Symposium

Coronary Plaque Regression and Compositional Changes by Lipid-Lowering Therapy: IVUS Substudy in Livalo® (Pitavastatin) in Acute Myocardial Infarction Study (LAMIS)

Livalo Acute Myocardial Infarction Study (LAMIS) Group :
Young Joon Hong, Myung Ho Jeong, Youngkeun Ahn, Tae Hoon Ahn, Jang Ho Bae, Seung Ho Hur, Seung Woon Rha, Kee Sik Kim, In Ho Chae, Jong Hyun Kim, Kyeong Ho Yun, Sang Wook Kim

Plaque Regression by Statin

- Atherosclerosis is usually viewed as a chronic progressive disease characterized by continuous accumulation of atheroma within the arterial wall.
- Intravascular ultrasound (IVUS) has emerged as the most sensitive and reliable measure of the progression of coronary disease.
- Prior angiographic and IVUS trials have shown reduced progression of coronary atherosclerosis with statin therapy.

Lipid Lowering and Plaque Regression: Monotherapy Studies

Study	Treatment group Regimen	LDL–C	Δ% Stenosis (*P*)	% Event reduction
NHLBI II	D + R	↓31	—	33
STARS	D + R	↓36	↓7.7(<0.01)	89
Heidelberg	D + E	↓8	↓4.0(0.05)	-27*
CCAIT	D + L	↓29	↓1.2 (0.039)	—
MARS	D + L	↓38	↓0.6	—
BECAIT	D + F	↓3	↓2.55	77
LCAS	D + Fl	↓24	↓2.0 (0.043)	33
Post-CABG	D + L	↓14	↓5.4 (0.001)	—

*A -27% reduction means a 27% increase (NS). D=diet; R=resin; E=exercise program; F=fibrate-type drug; Fl=fluvastatin; L=lovastatin.

Levine GN et al. *N Engl J Med*. 1995;332:512-521.

Brown BG, Fuster V. In Fuster V et al, eds. *Atherosclerosis and Coronary Artery Disease.* Philadelphia, Lippincott-Raven, p. 194.

Jukema JW et al. *Circulation*. 1995;91:2528-2540.

Post-CABG Investigators. *N Engl J Med*. 1997;336:153-162.

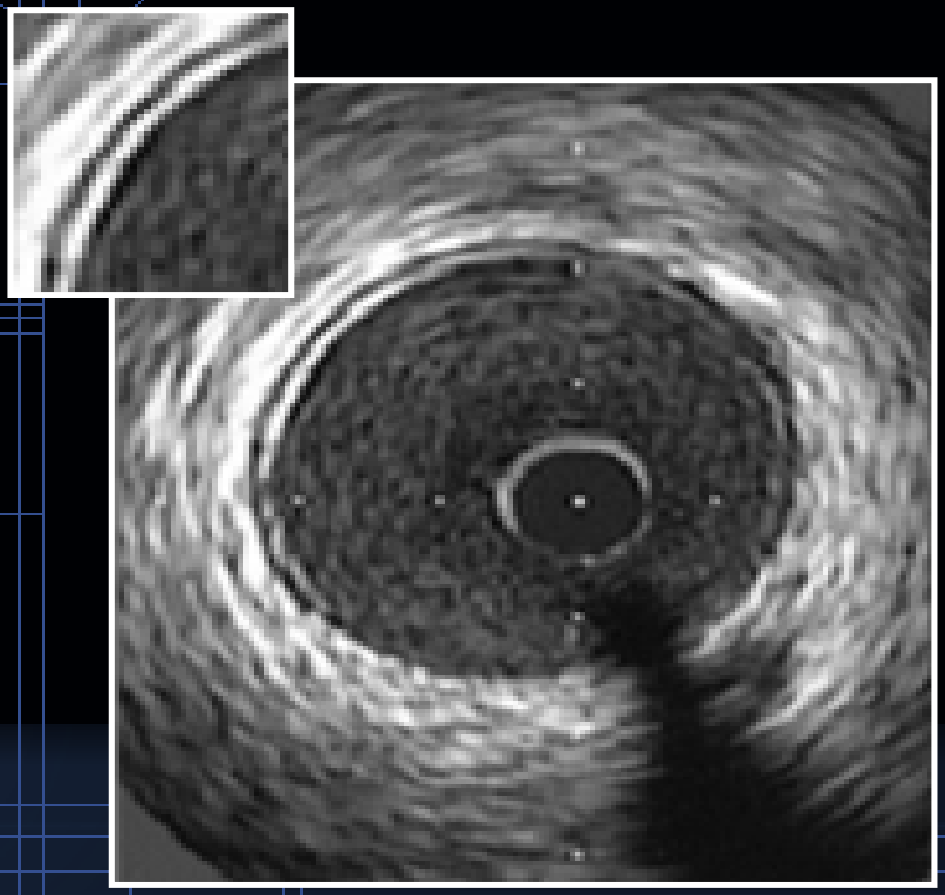
Lipid Lowering and Plaque Regression: Combination Therapy Studies

Study	Treatment group Regimen	LDL	Δ% Stenosis (*P*)	% Event reduction
CLAS I	D + R + N	↓43	—	25
POSCH (5y)	D + PIB ± R	↓42	—	35 (62)
Lifestyle	V + M + E	↓37	↓2.2 (0.001)	—
FATS (N+C)	D + R + N	↓32	↓0.9 (0.005)	80
FATS (L+C)	D + R + L	↓46	↓0.7 (0.02)	70
CLAS II	D + R + N	↓40	—	43
USCF-SCOR	D + R + N ± L	↓39	↓1.5 (0.04)	—
SCRIP	D+(R+N+L+F)+E, BP	↓21	—	50
HARP	D+P+N+C+F	↓41	↑2.1	33
Post-CABG	D+L+C	↓37-40	↓0.054	29

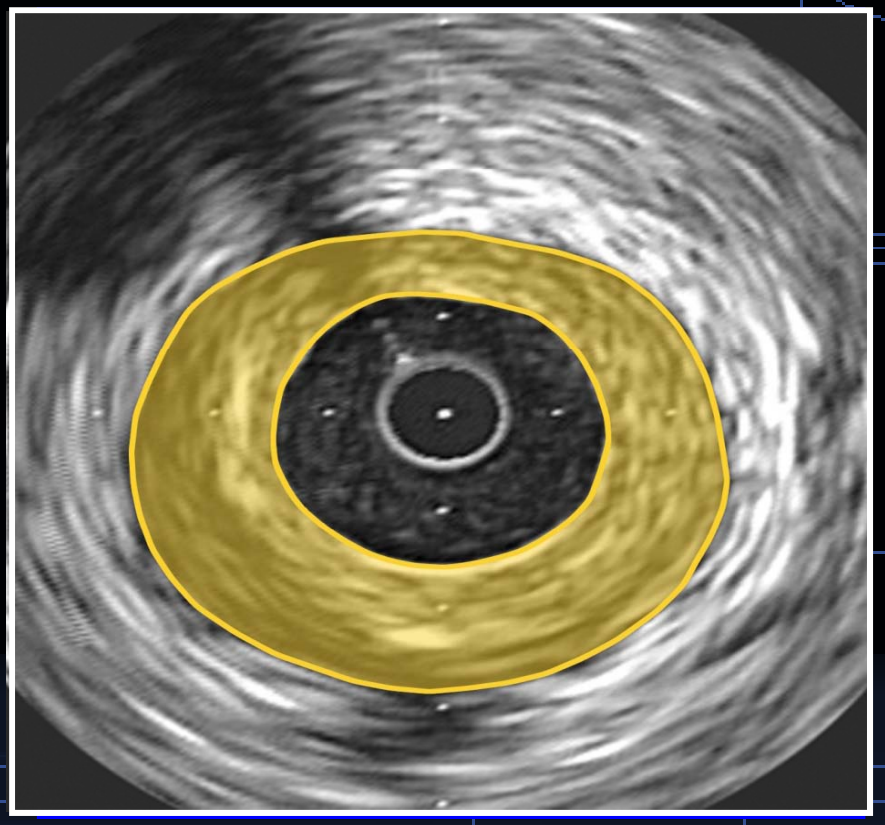
C=cholestyramine; D=diet; E=exercise program; F=fibrate-type drug; L=lovastatin; M=relaxation techniques; N=nicotinic acid; P= pravastatin; PIB=partial ileal bypass; R=resin; V=vegetarian diet.

Levine GN et al. *N Engl J Med.* 1995;332:512-521.
Brown BG, Fuster V. In: Fuster V et al, eds. *Atherosclerosis and Coronary Artery Disease.* Philadelphia, Lippincott-Raven, p. 194.

IVUS: Normal and diseased anatomy

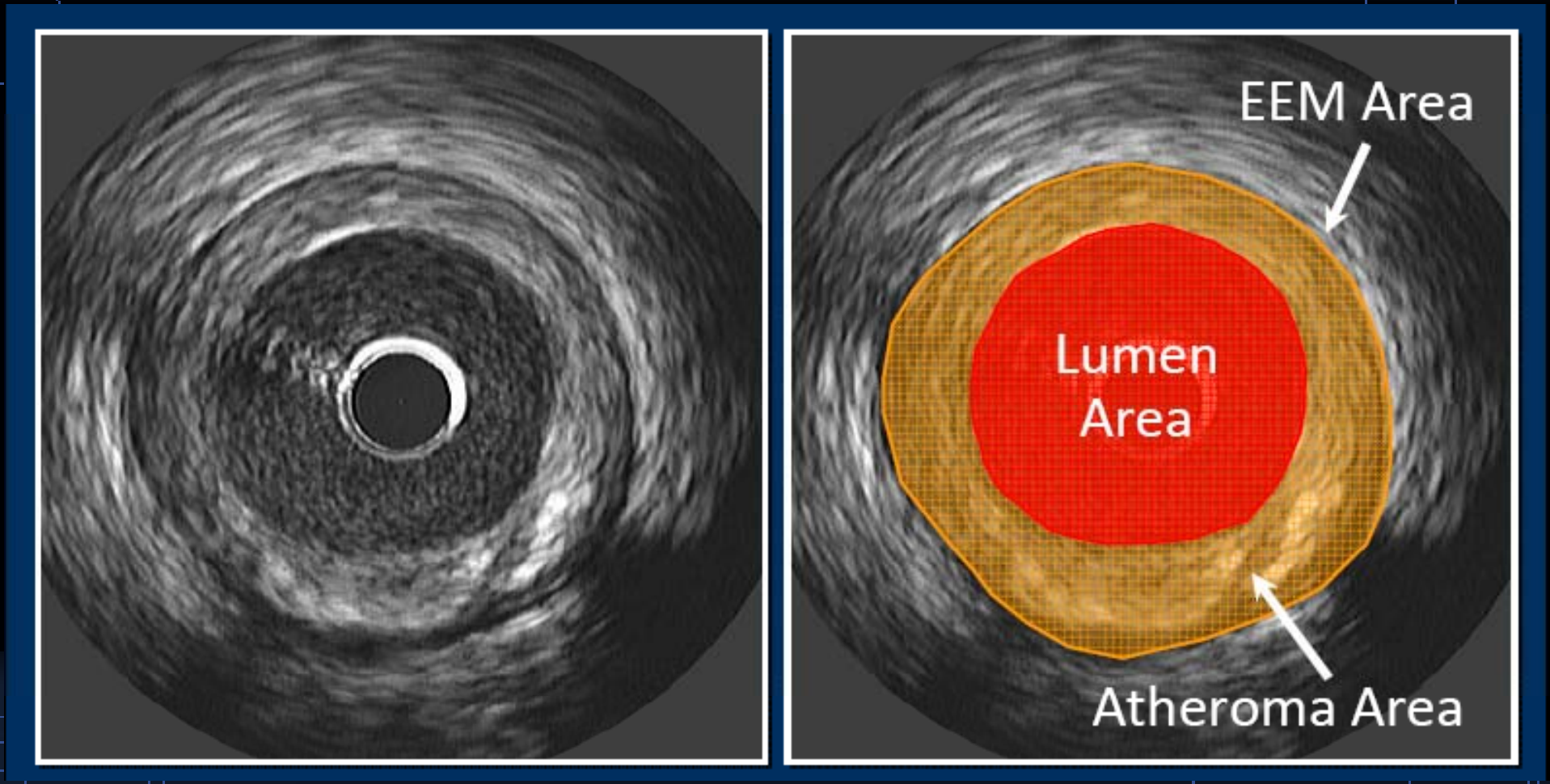


Normal Anatomy



Concentric Disease

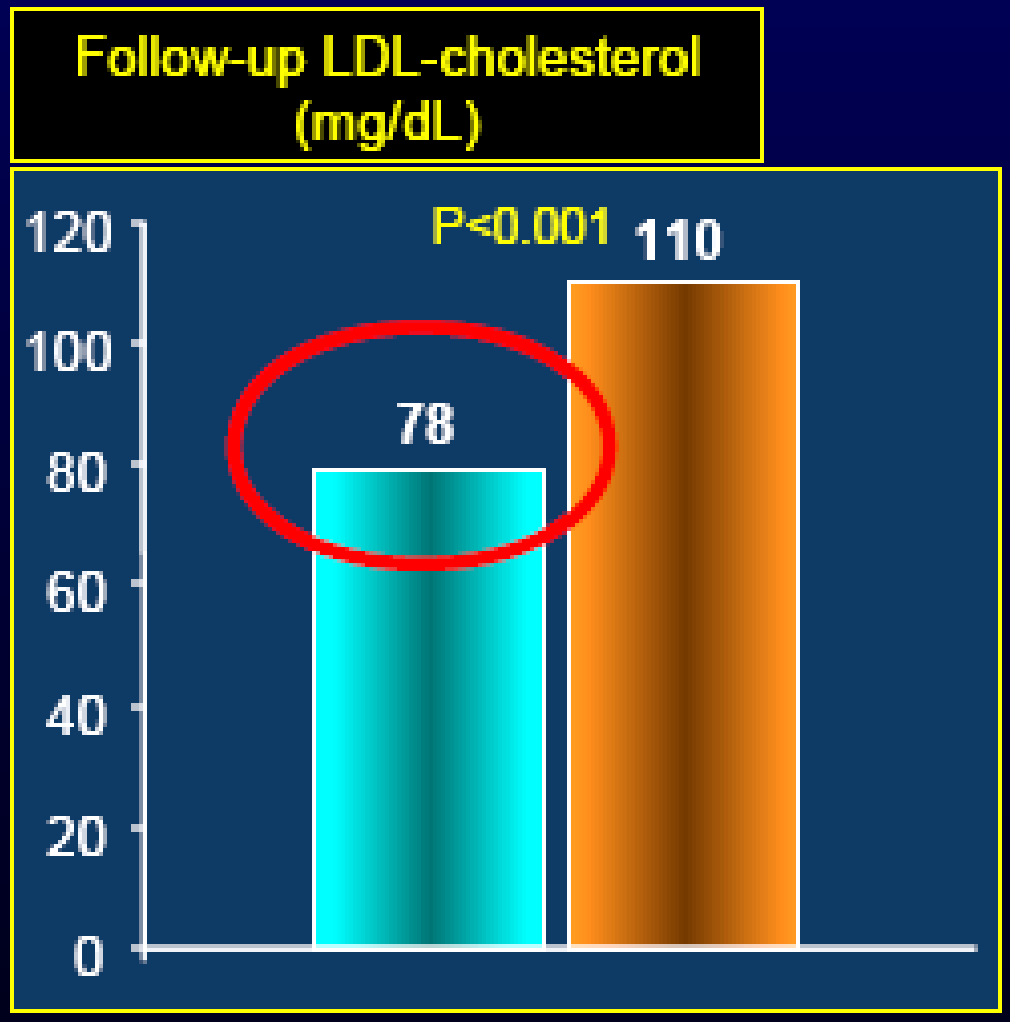
Analysis of atheroma area

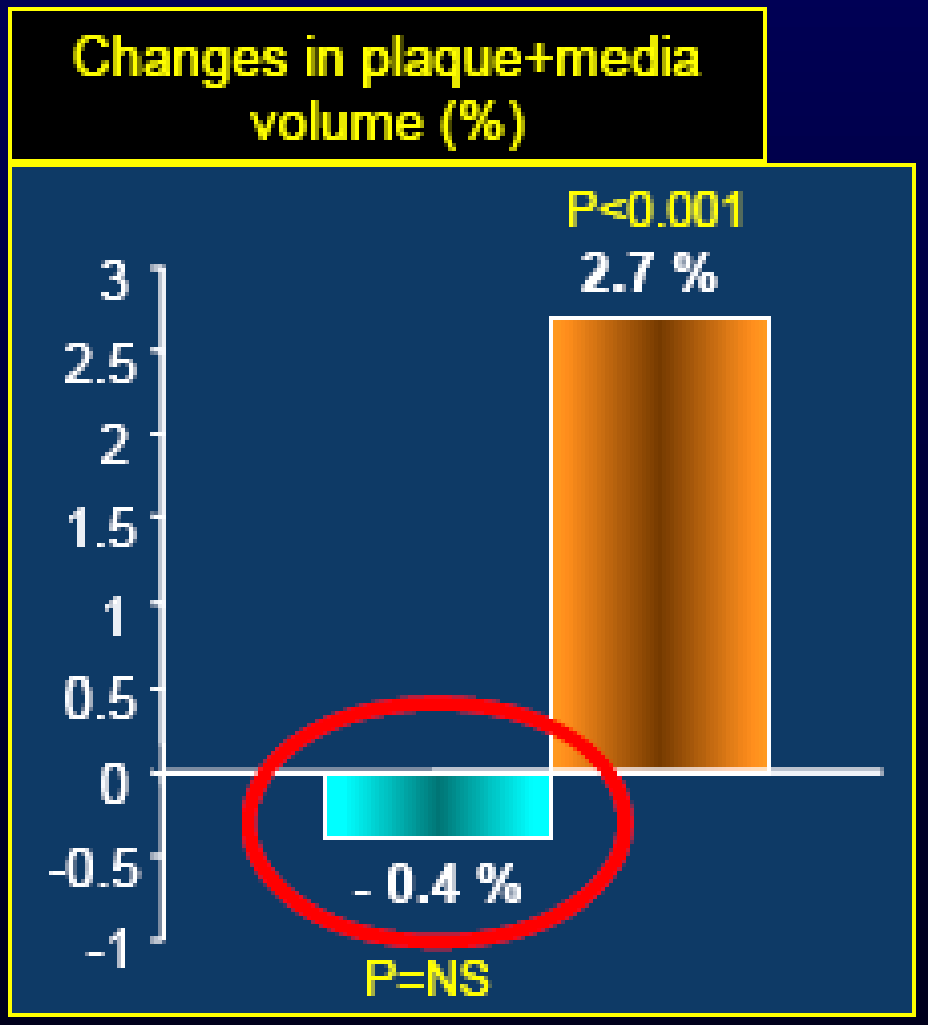


Atheroma area = (EEM area) – (Lumen area)

REVERSAL Trial

(502 patients w./CAD and elevated LDL-C; randomized, double-blind, multicenter trial)





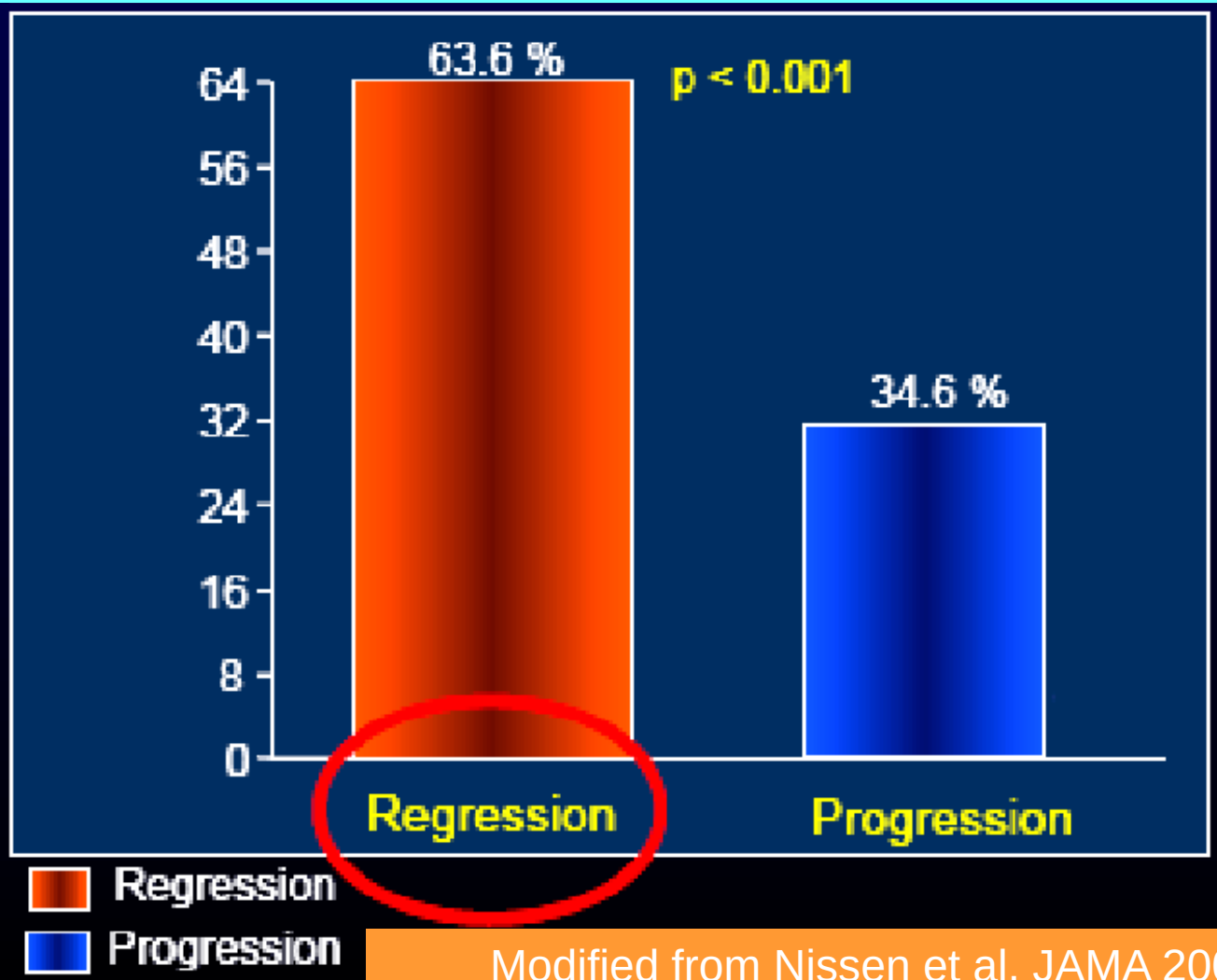
80 mg Atorvastatin (n=253)

40 mg Pravastatin (n=249)

modified from Nissen et al. (REVERSAL) JAMA 2004;291:1071-80

ASTEROID Trial (40mg Rosuvastatin)

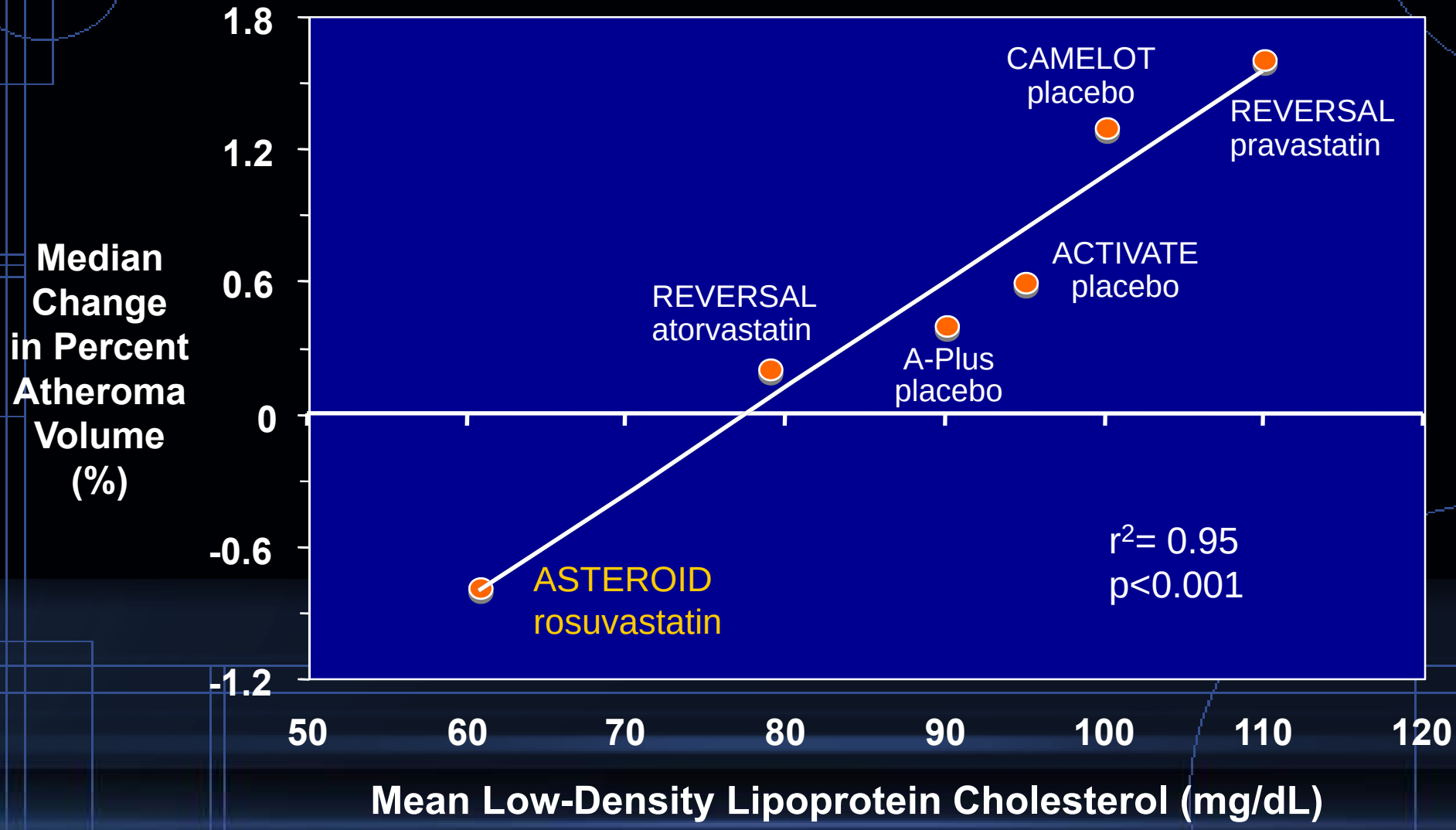
Frequency of Regression vs. Progression of Plaque Volume (%)



Modified from Nissen et al. JAMA 2006:295;1556-65

Recent Coronary IVUS Progression Trials

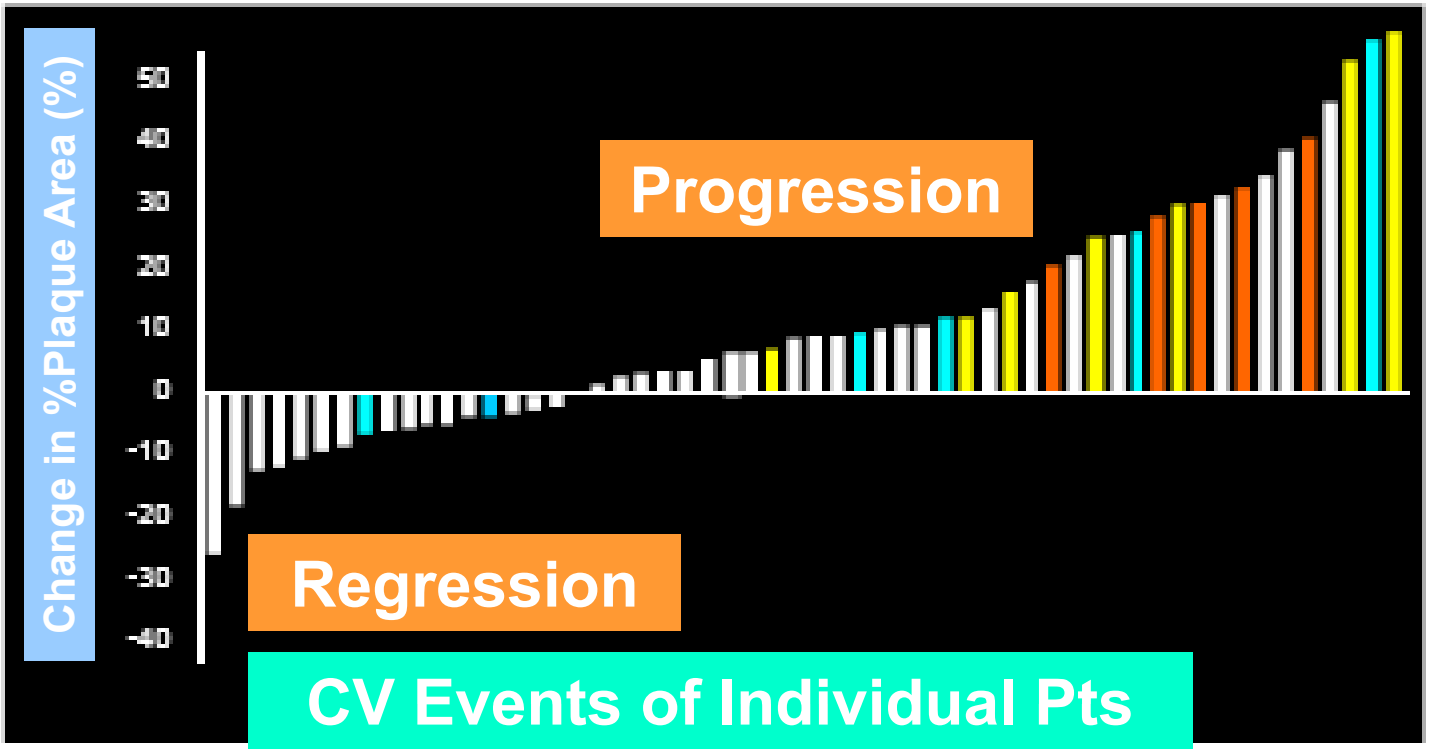
Relationship between LDL-C and Progression Rate



Basis for Study of Atheroma Burden

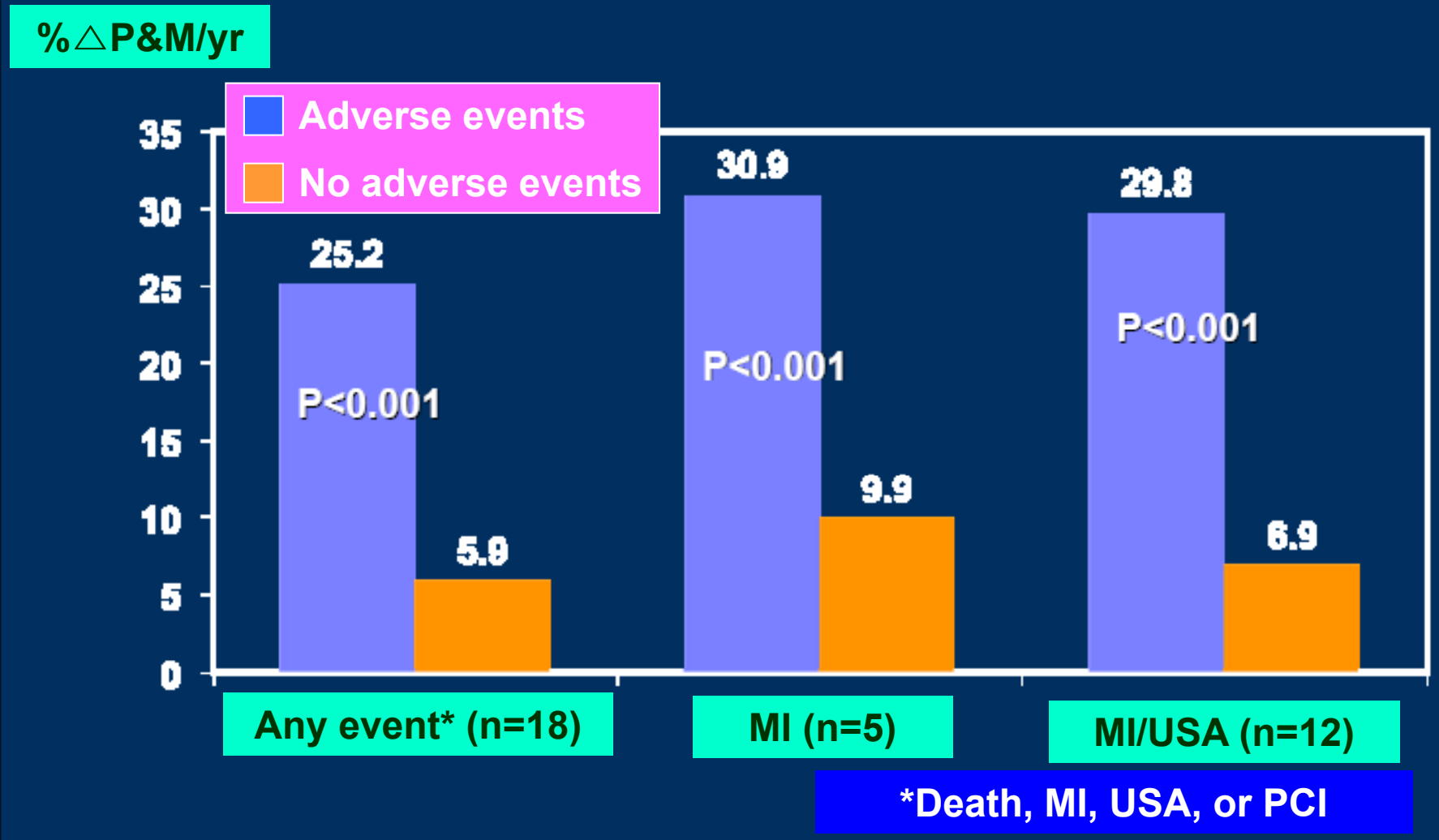
- Autopsy studies reveal greater plaque burden in cardiac versus non-cardiac death
- Angiography and IMT in large populations spanning full spectrum of risk demonstrate relationship between burden and outcome
- Therapies that slow progression on these modalities typically reduce events

IVUS Plaque Progression vs. Actual CV Events



Modified from von Birgelen et al. Circulation 2004:110;1579-85

Relationship Between Plaque Progression and Clinical Events



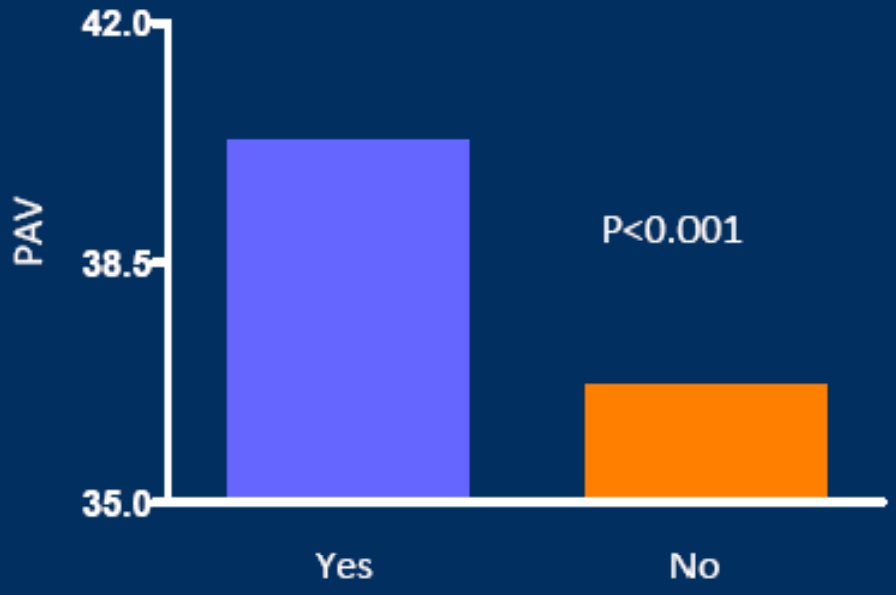
von Birgelen *Circulation* 2004; 110:1579-85

Atheroma Burden and Incident Clinical Events

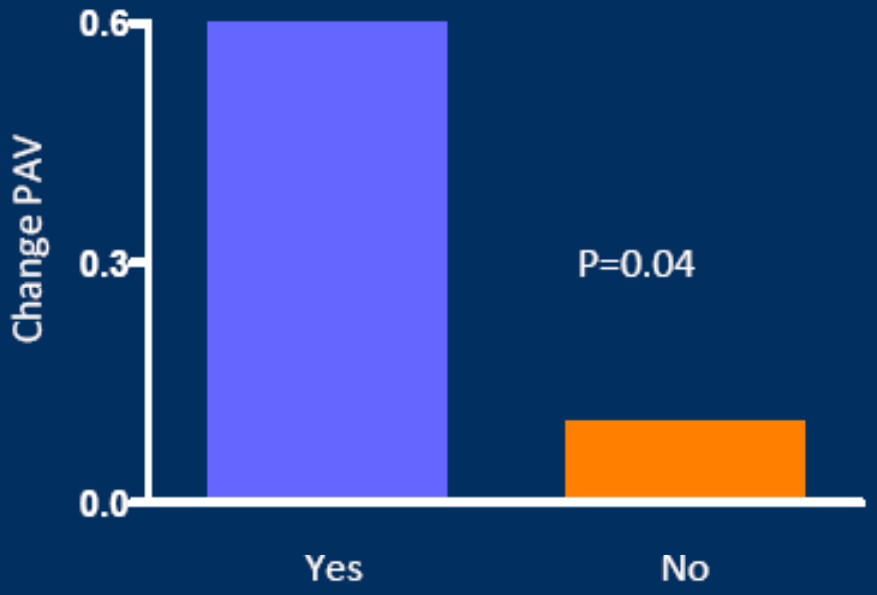
ILLUSTRATE (n=1180)

Incidence of cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke and coronary revascularisation

Baseline Percent Atheroma Volume



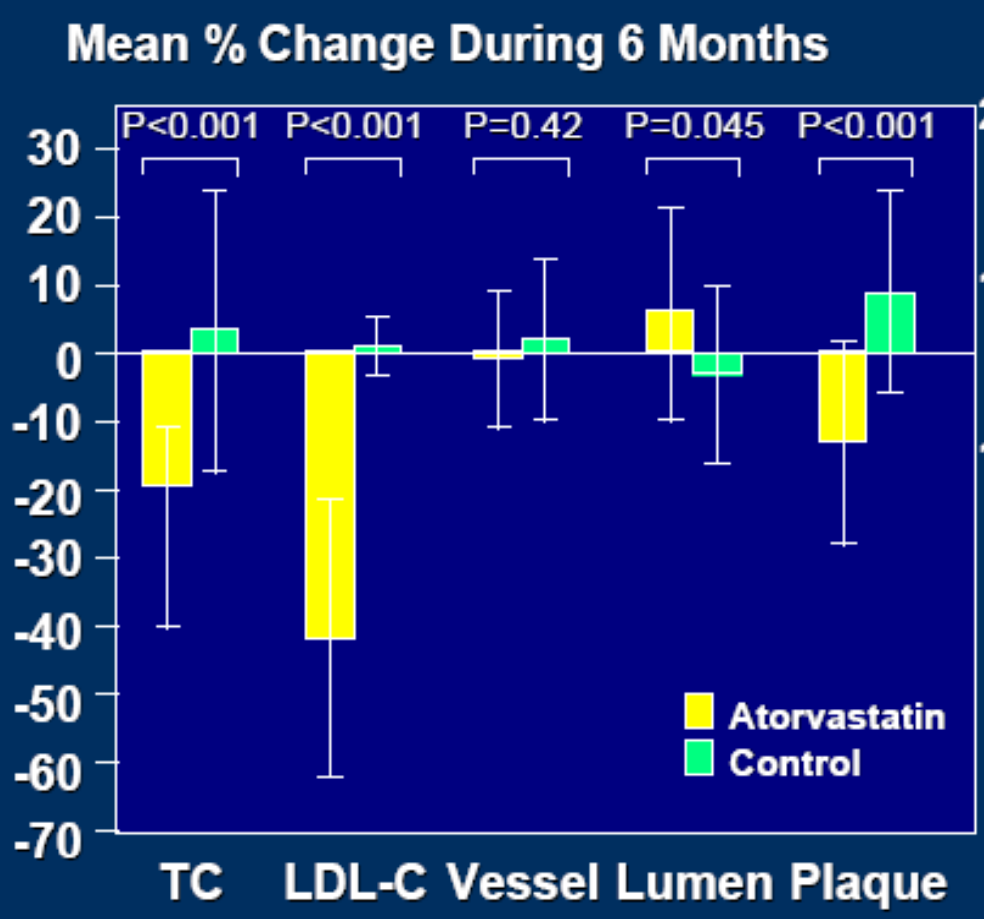
Change Percent Atheroma Volume



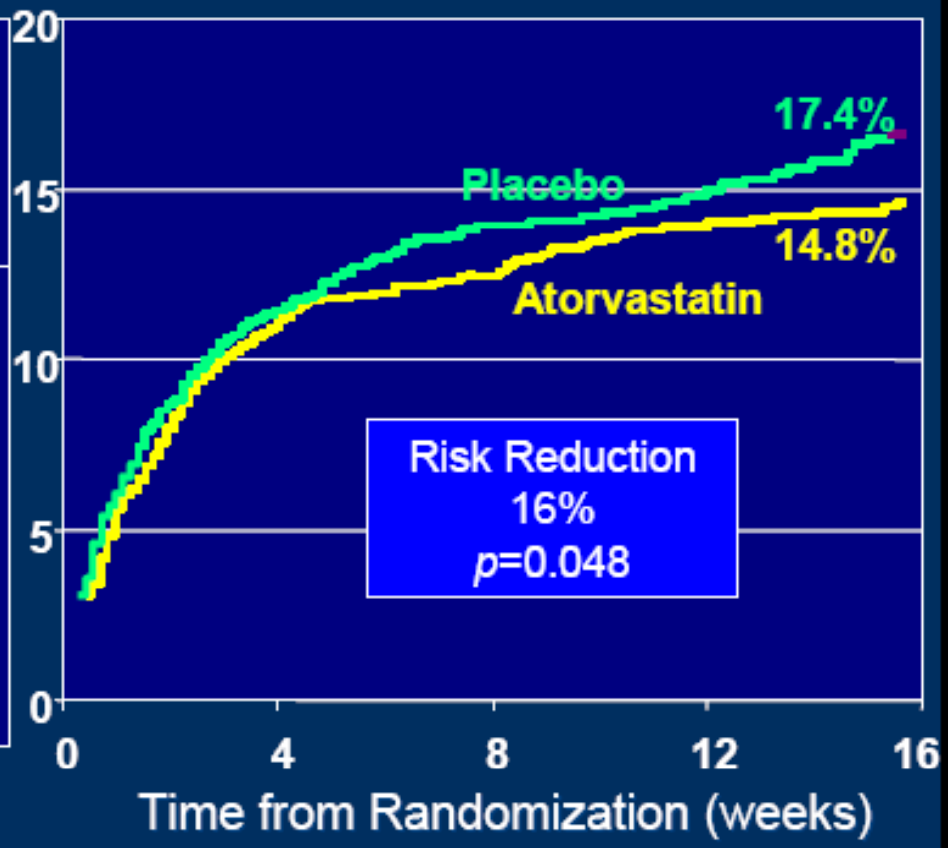
Nicholls *AHA Scientific Sessions* 2007

Link Between Imaging and Outcome

ESTABLISH

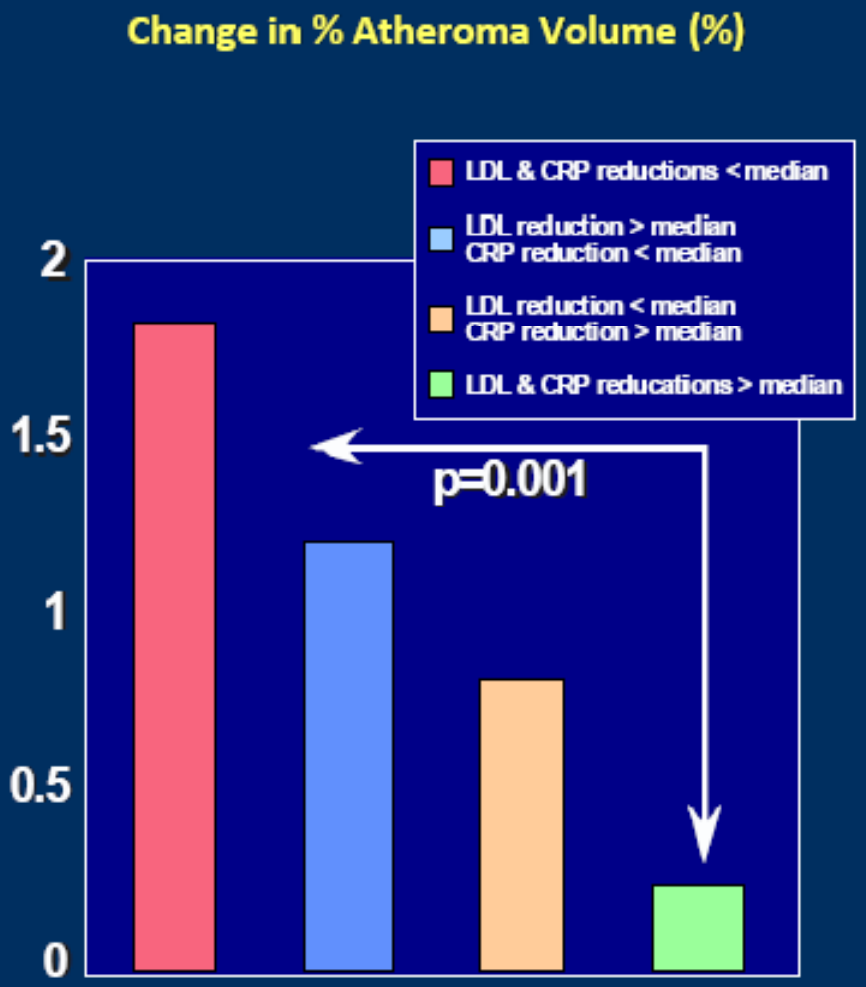


MIRACL

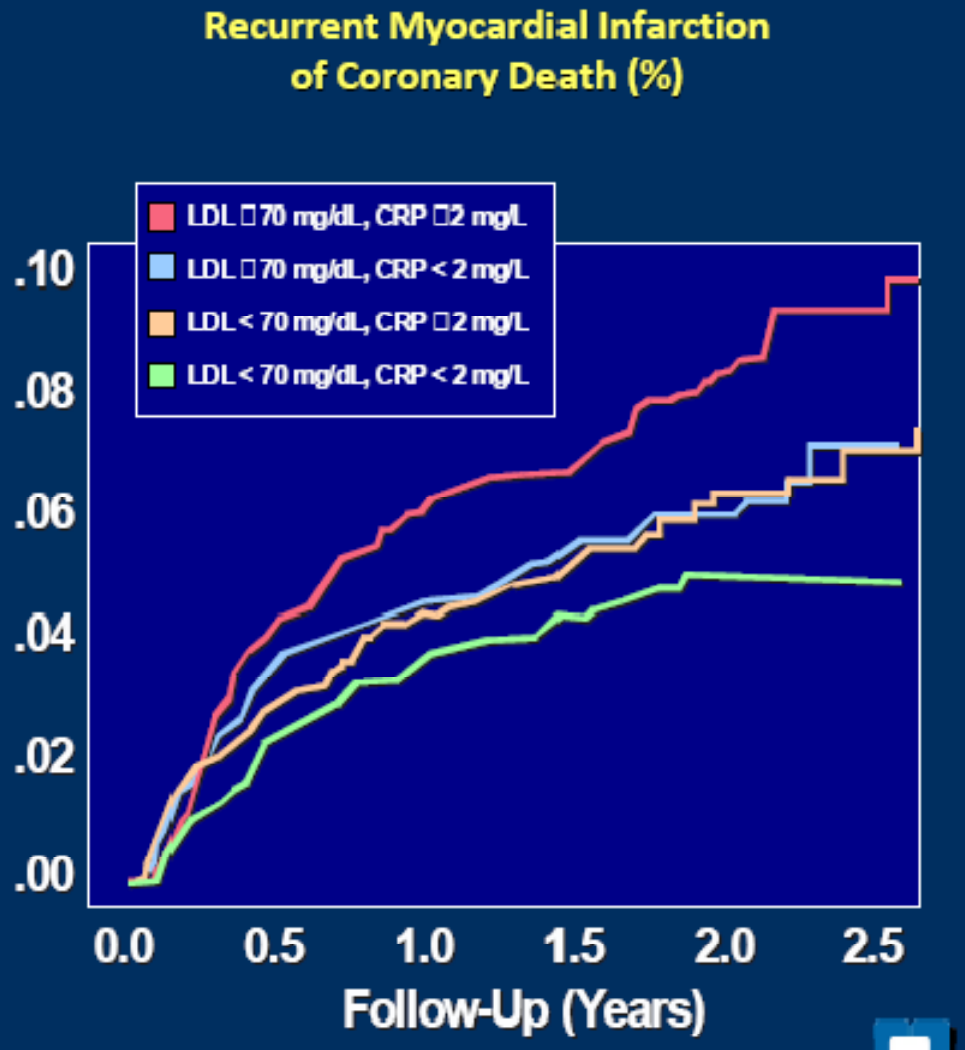


Okazaki et al., Circulation 2004;110:1061-68

Complementary Impact on Plaque Progression and Clinical Events



REVERSAL

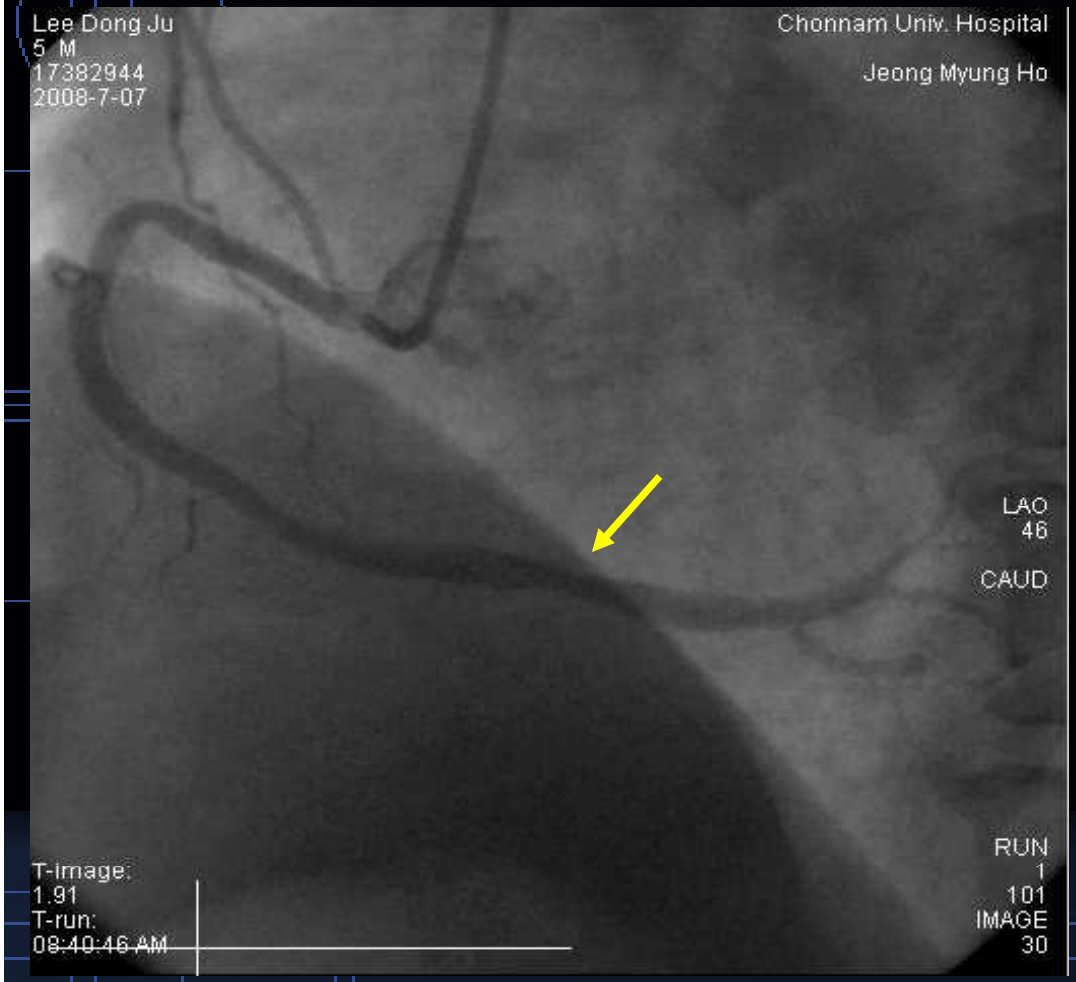


PROVE IT - TIMI 22

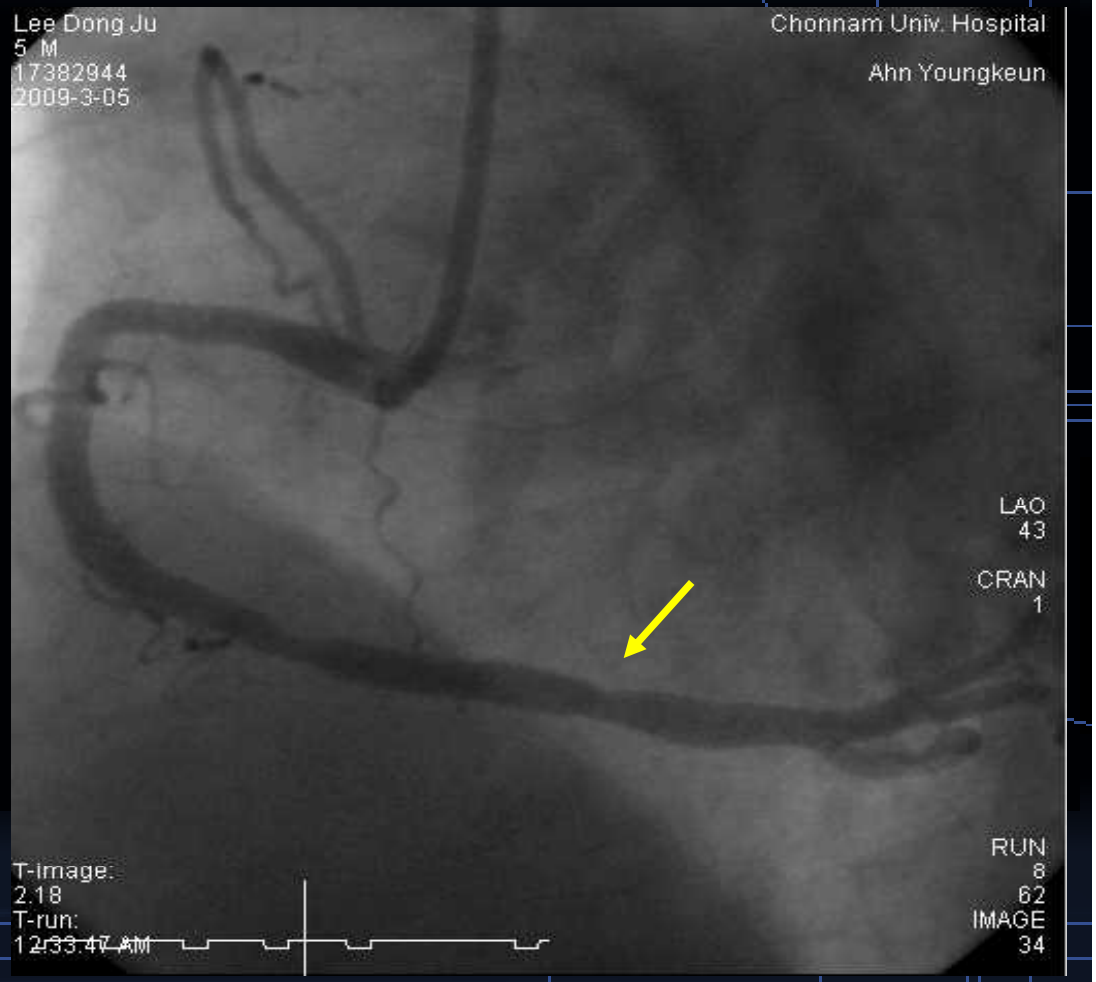
The Effect of Rosuvastatin 20 mg and Atorvastatin 40 mg on Plaque Regression in Patients with Mild to Moderate Degree of Coronary Stenosis

Hong YJ et al., Korean Circ J 2008;38:366-373, Presented at AHA 2009

Baseline

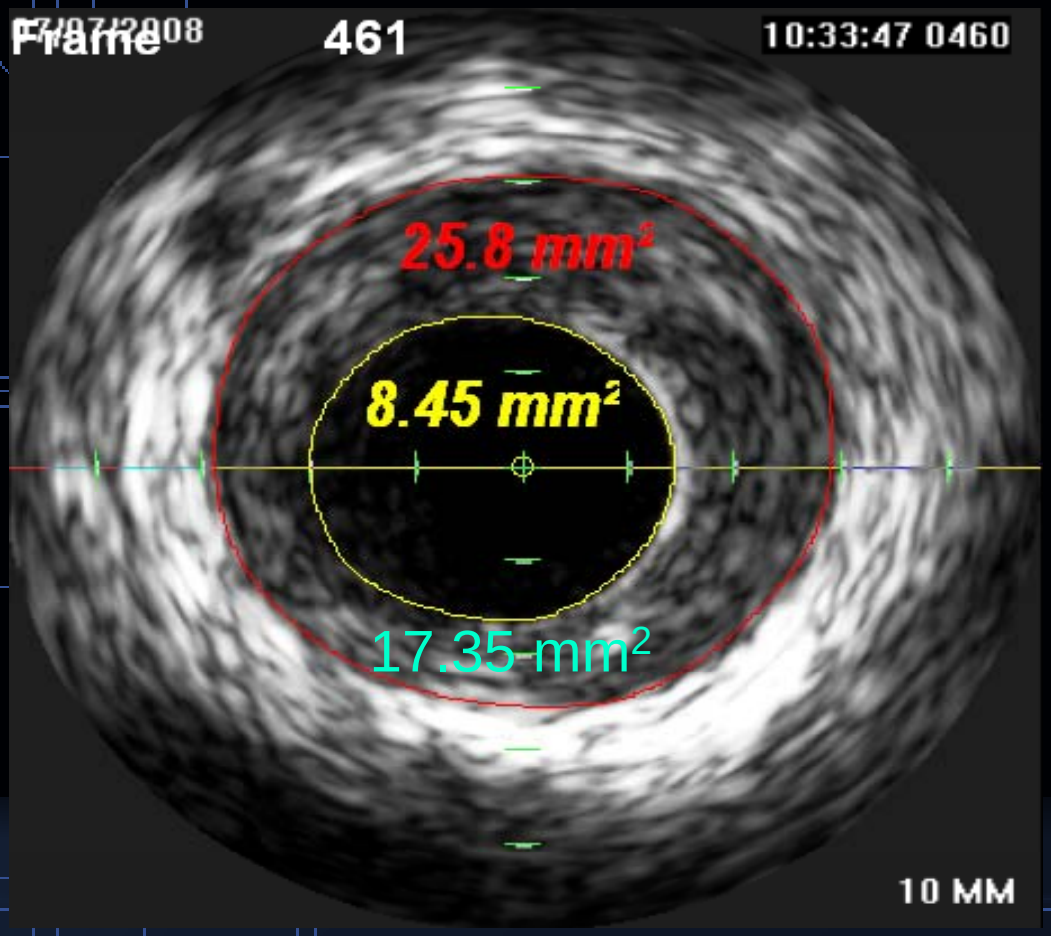


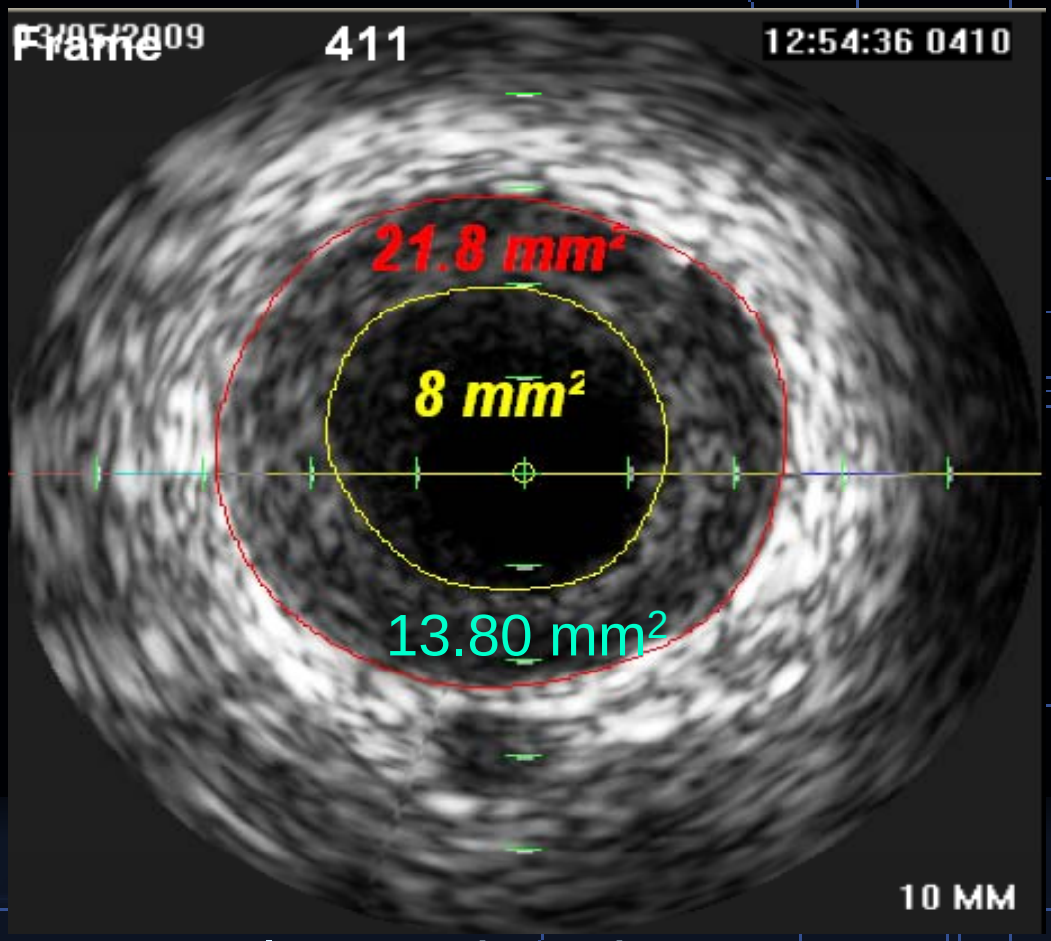
Follow up



Baseline

Follow up





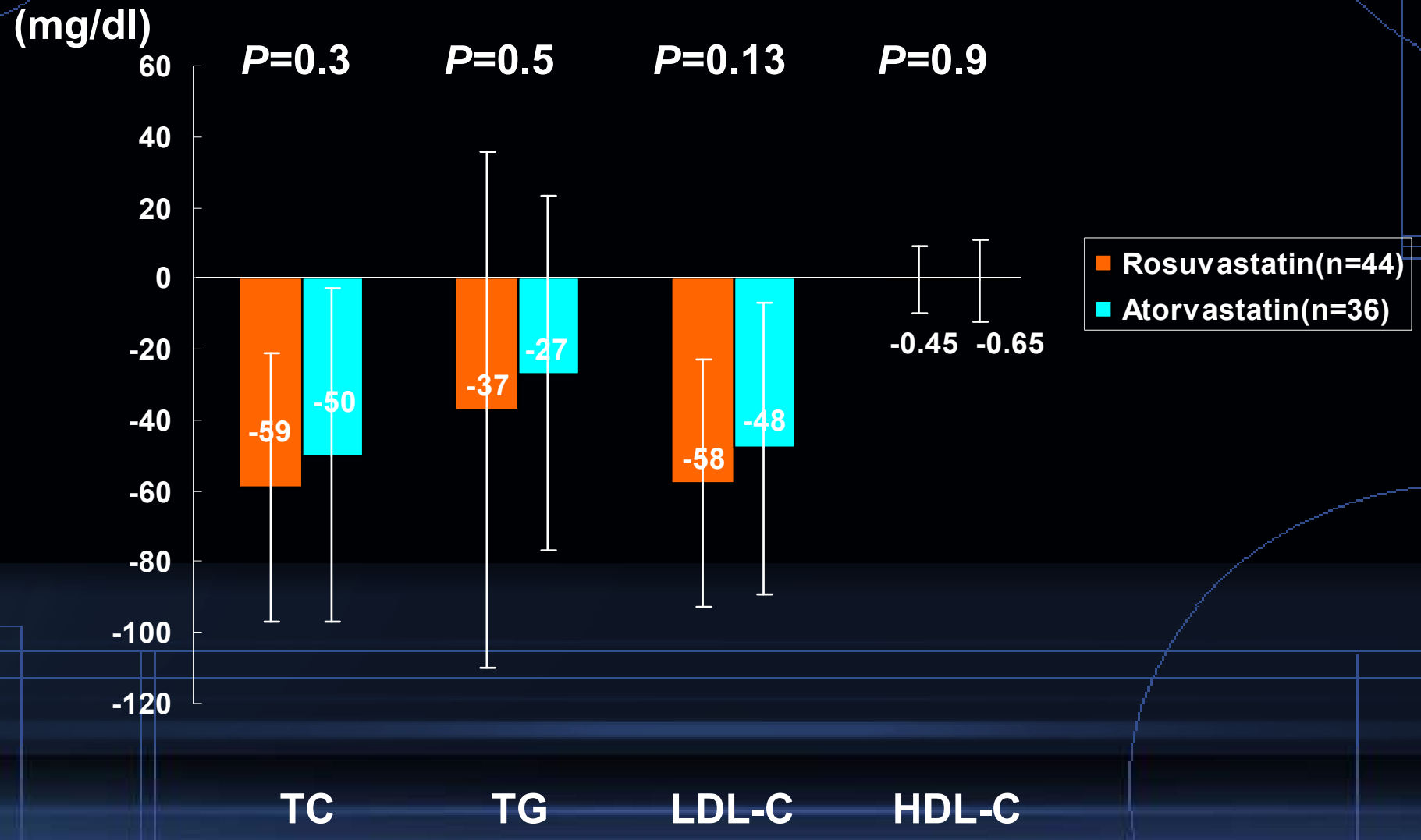
Plaque burden 67%

Plaque burden 63%

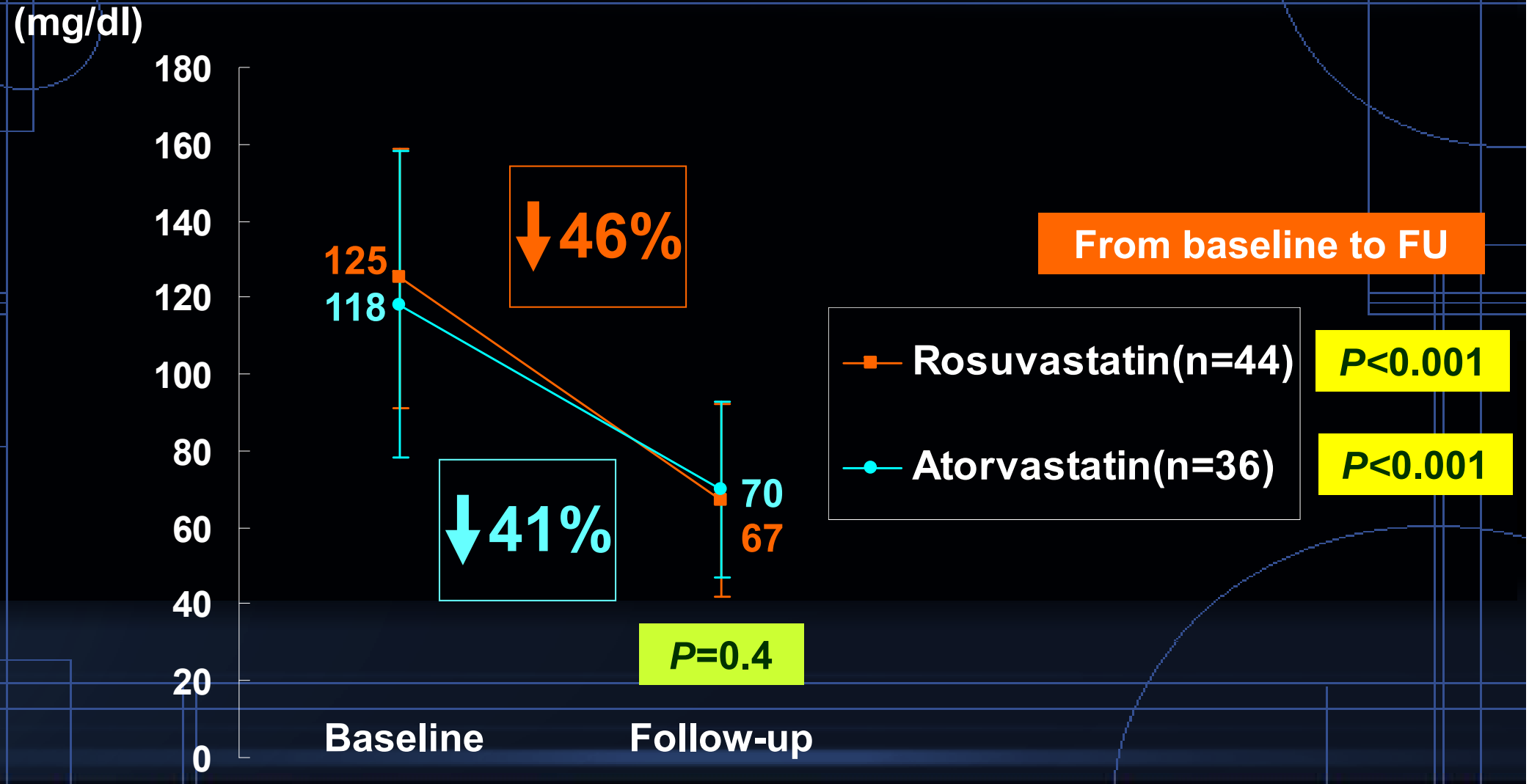
Rosuvastatin 20mg/d

Changes of Lipid Profiles at Follow-up

Follow-up duration: 11.0±6.9 months in Rosuvastatin vs. 11.3±8.1 months in Atorvastatin



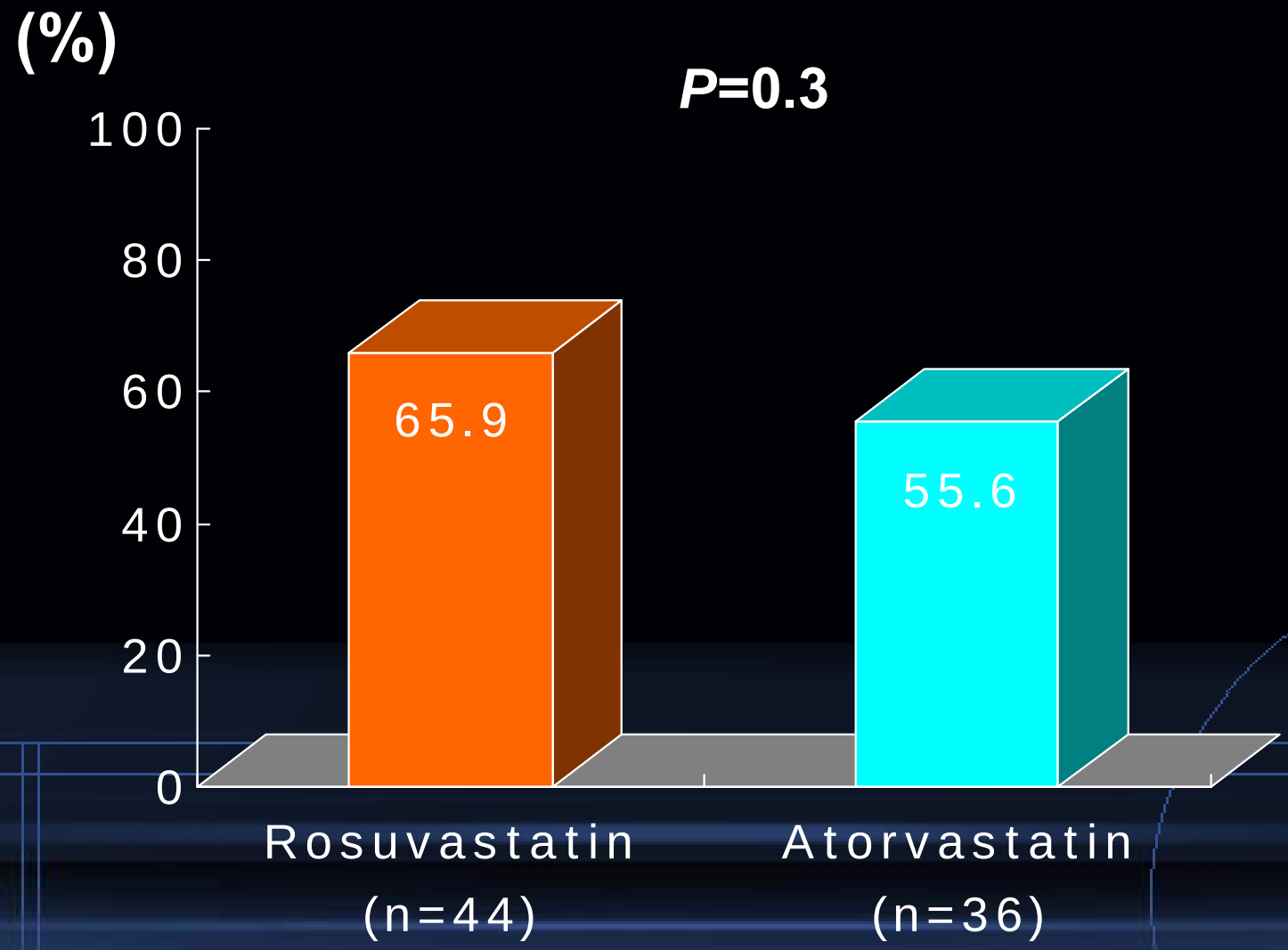
Changes of LDL-Cholesterol at Follow-up



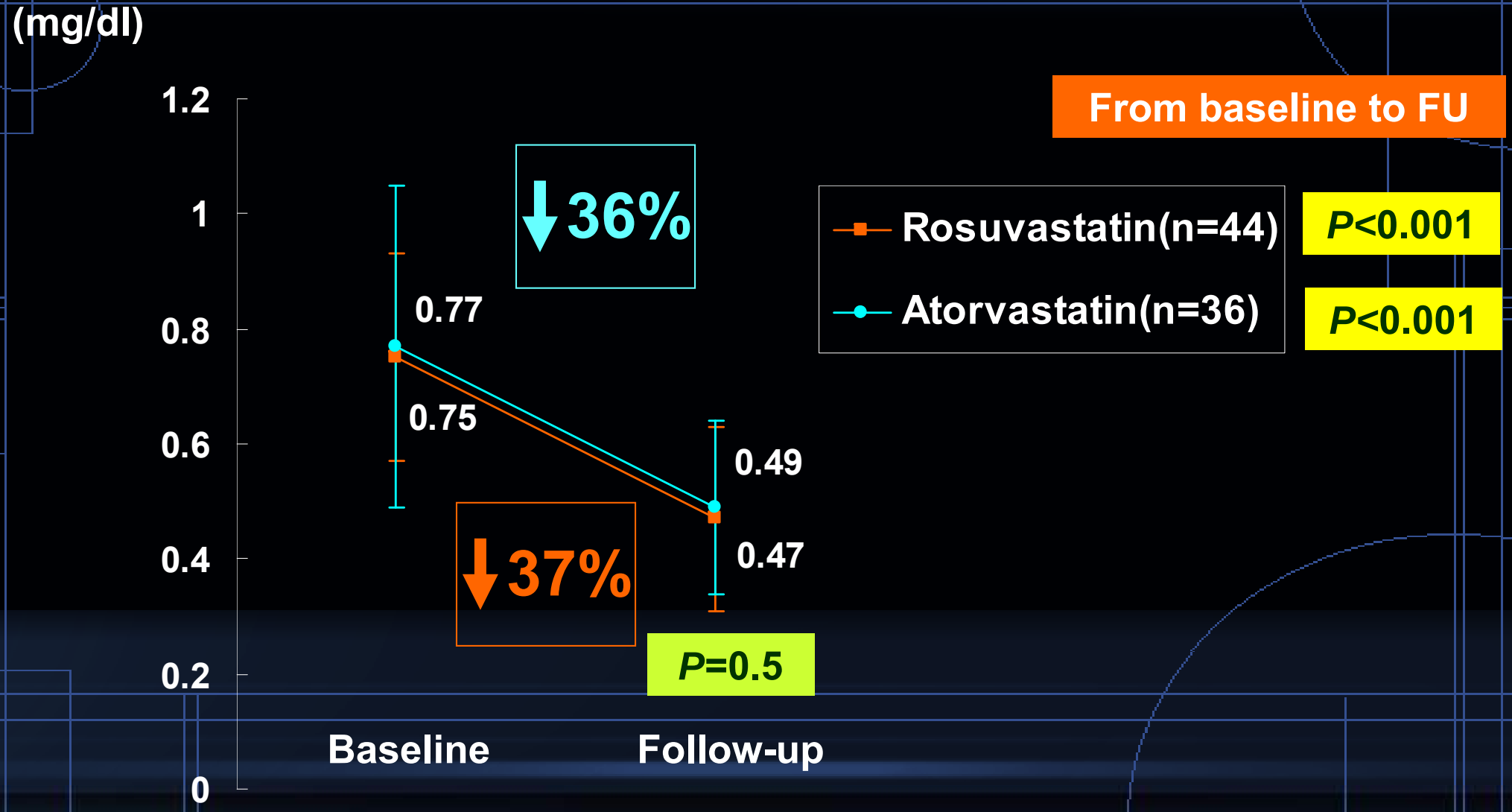
Follow-up duration: 11.0±6.9 months in Rosuvastatin vs. 11.3±8.1 months in Atorvastatin

Follow-up LDL-Cholesterol < 70mg/dl

Follow-up duration: 11.0±6.9 months in Rosuvastatin vs. 11.3±8.1 months in Atorvastatin



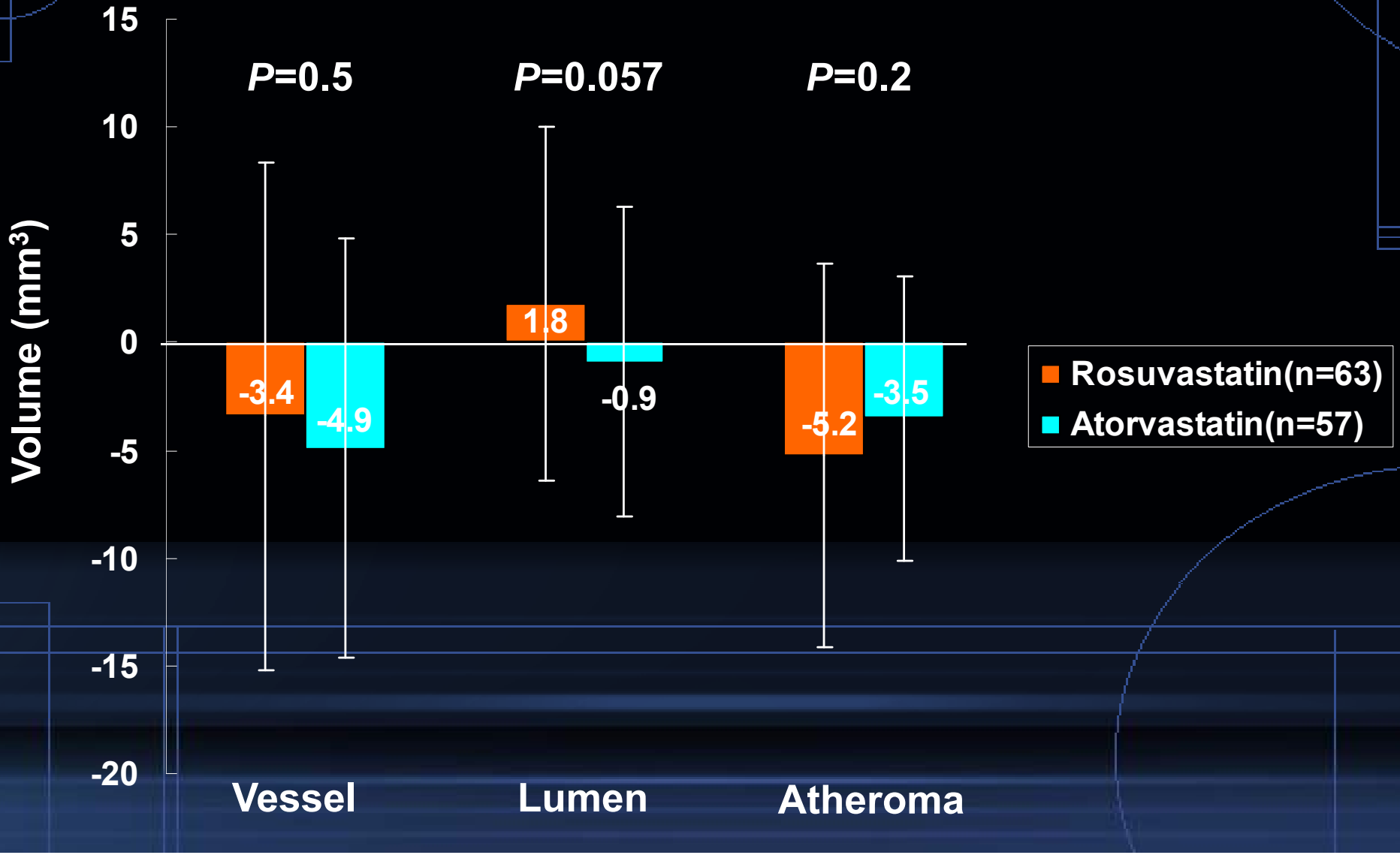
Changes of Apo-B/A1 at Follow-up



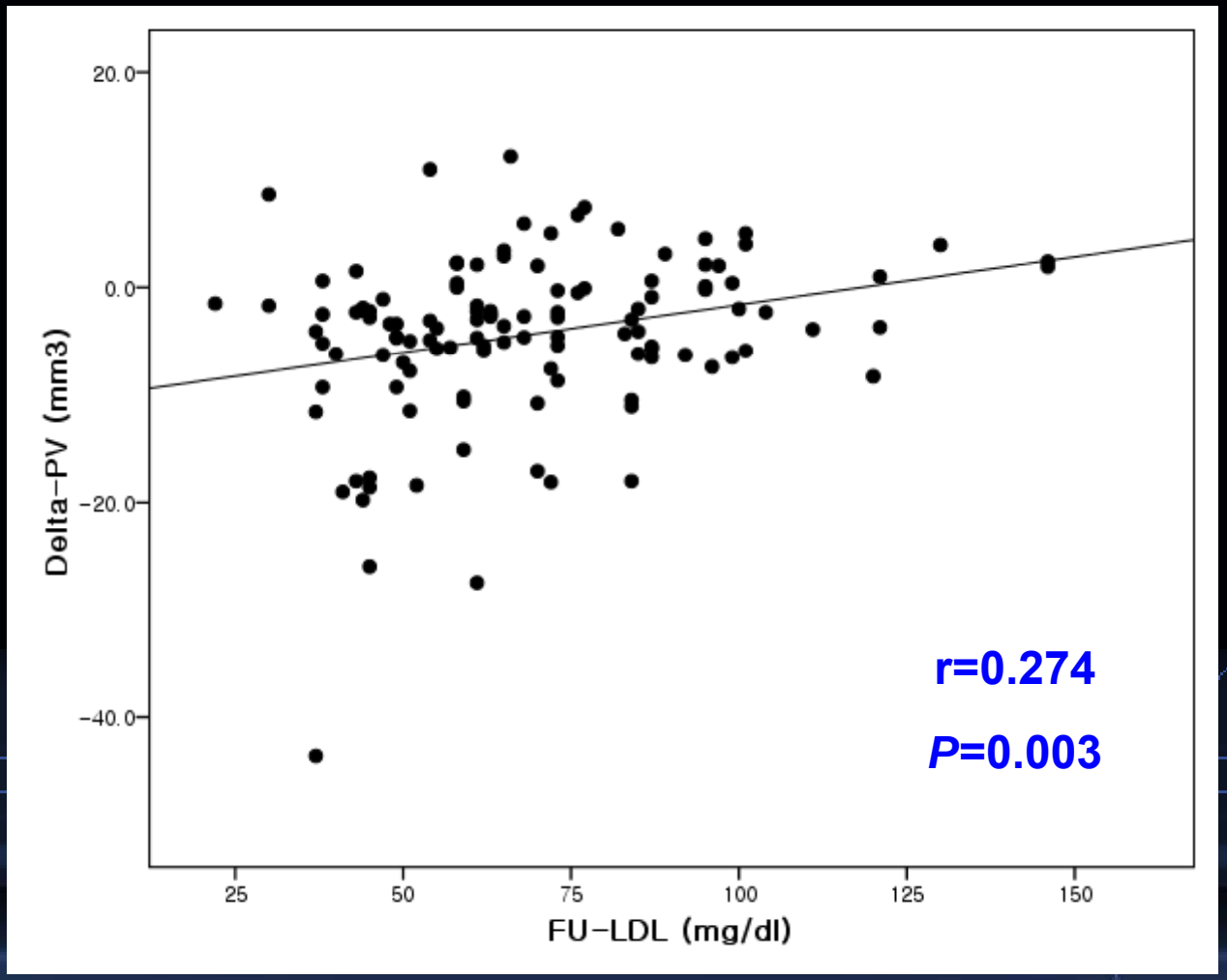
Follow-up duration: 11.0±6.9 months in Rosuvastatin vs. 11.3±8.1 months in Atorvastatin

Changes of Volumetric IVUS Parameters at Follow-up

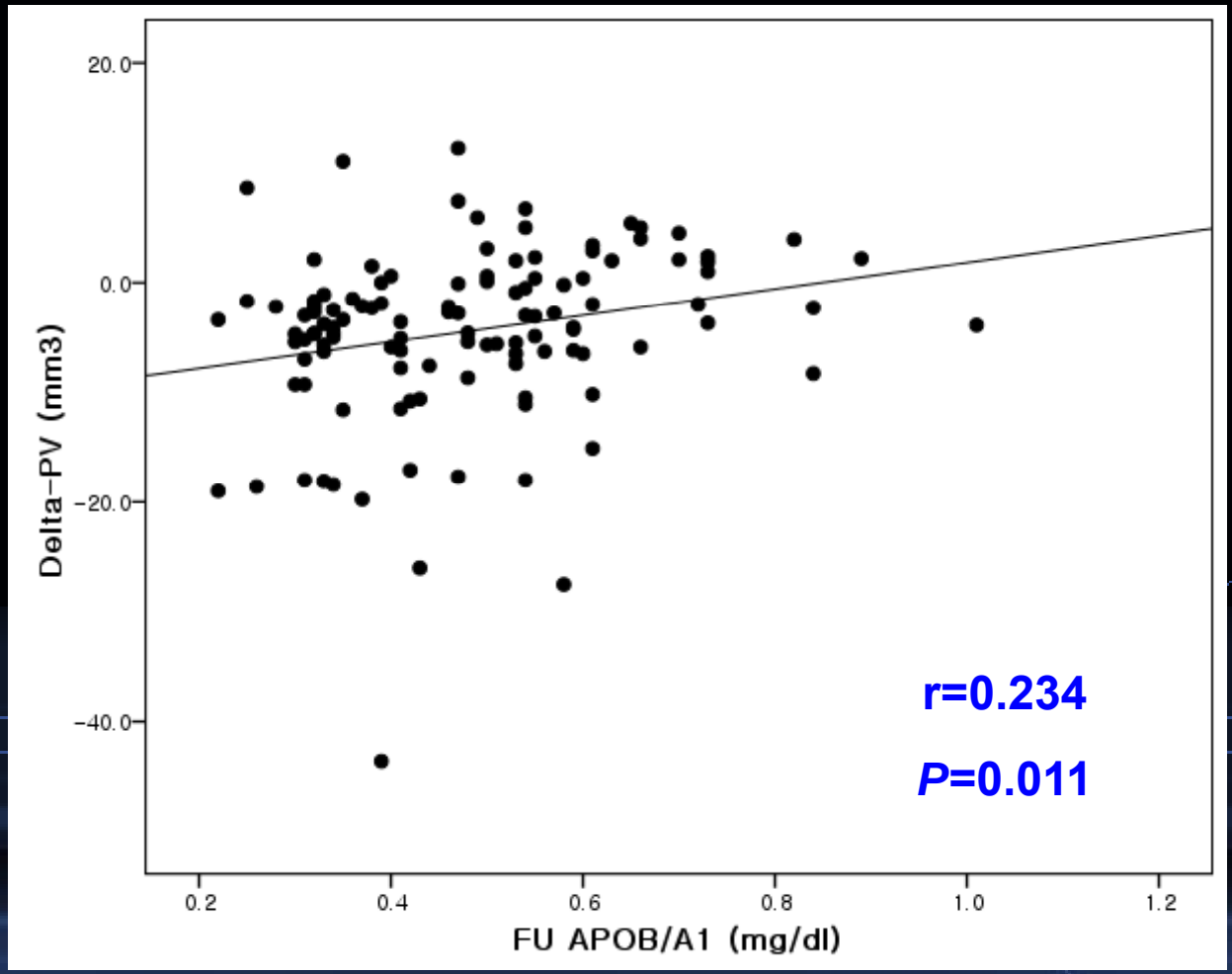
Follow-up duration: 11.0±6.9 months in Rosuvastatin vs. 11.3±8.1 months in Atorvastatin



Correlation Between Follow-up LDL-C and ΔAtheroma Volume



Correlation Between Follow-up Apo B/A1 and ΔAtheroma Volume



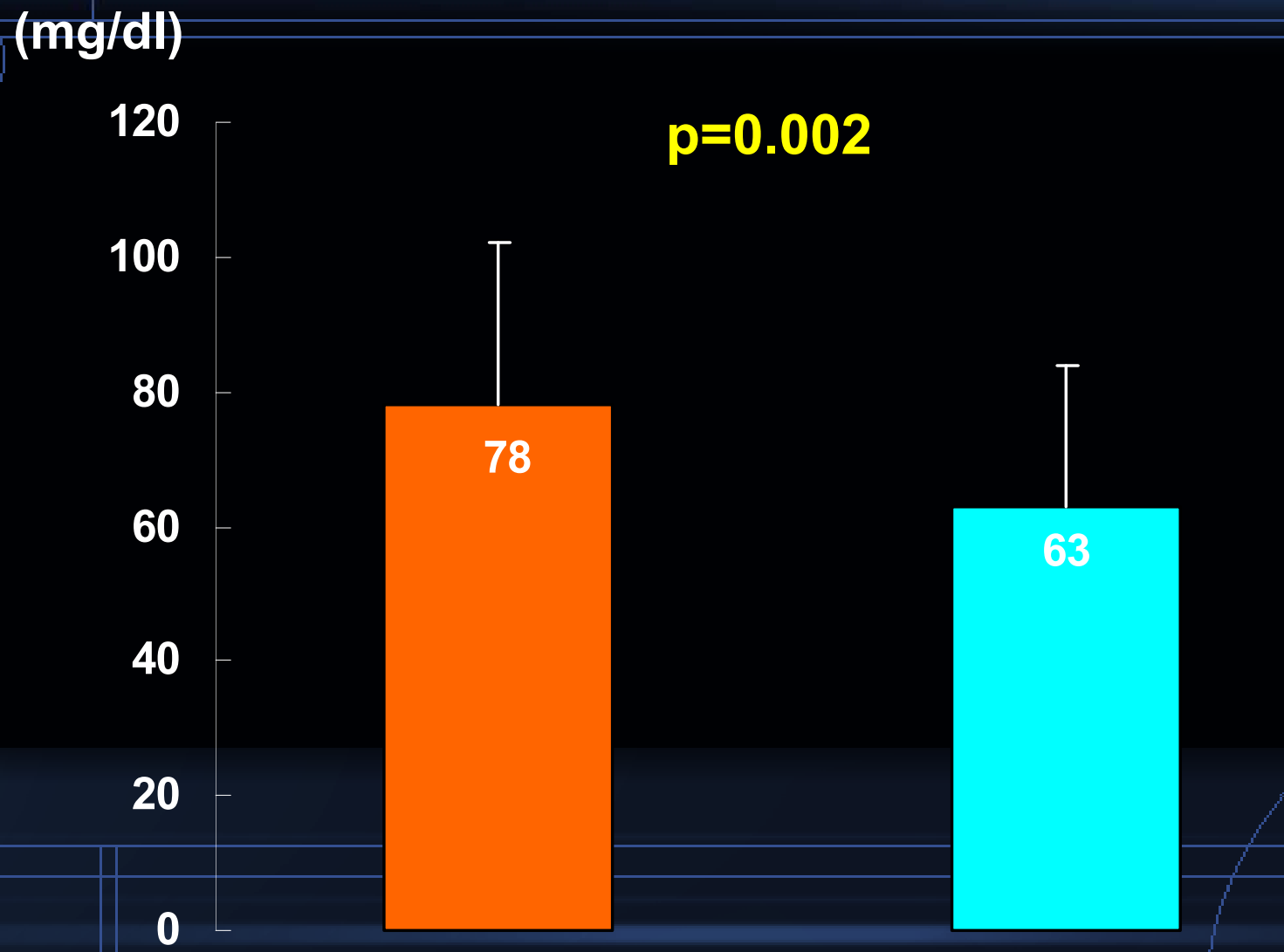
Conclusion – Plaque Regression by Statin in Native Coronary Artery

Both rosuvastatin 20 mg and atorvastatin 40 mg could contribute to the regression in Korean patients with mild to moderate stenosis.

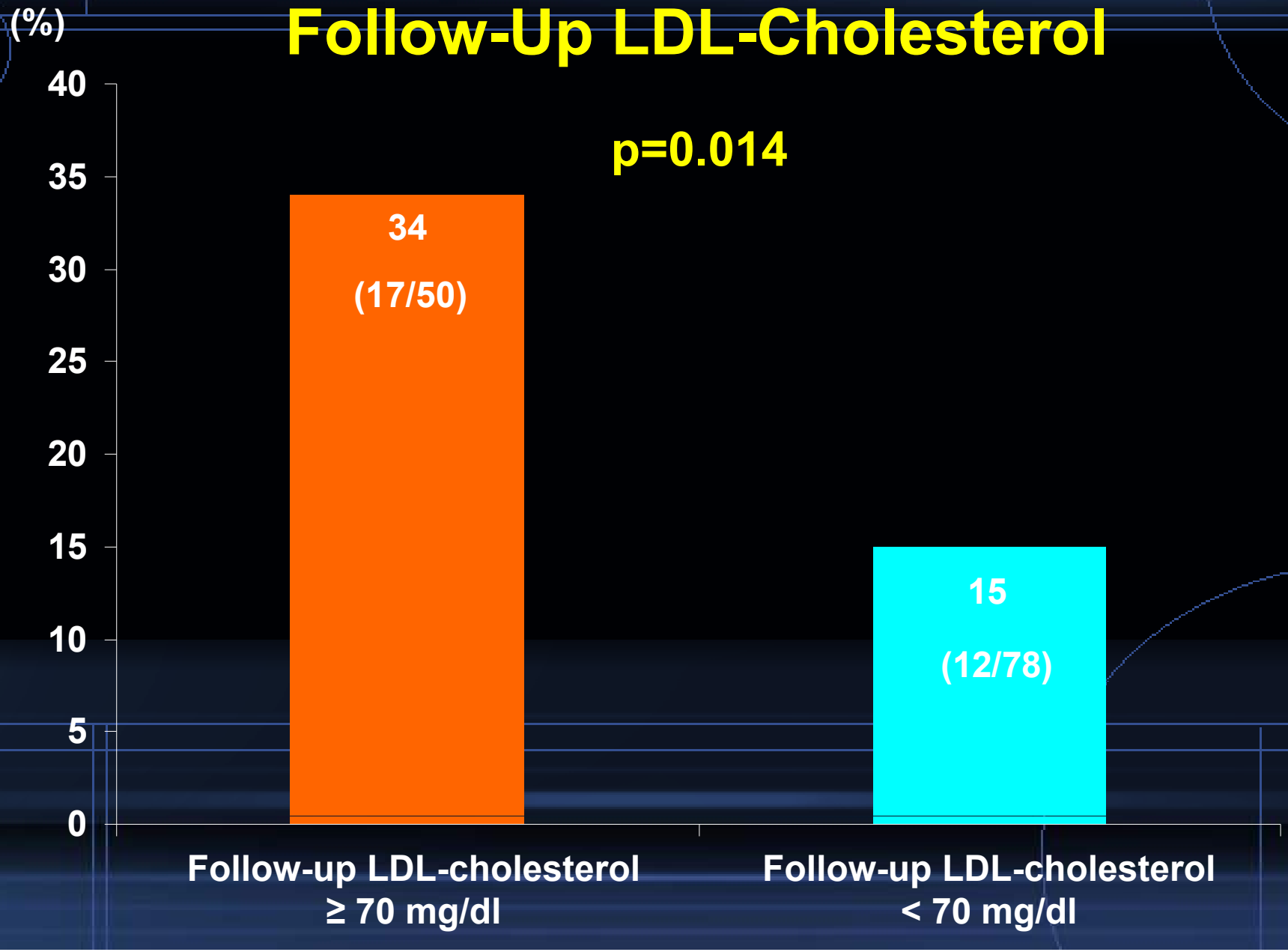
Laboratory Findings vs. Plaque Progression in Patients Who Use Moderate Dose of Statins

- 128 patients who underwent baseline and follow-up IVUS (mean 11 months) for non-intervened intermediate coronary stenosis
- 66 patients received 20mg/day of rosuvastatin and 62 patients received 40mg/day of atorvastatin from baseline to follow-up.
  - Plaque volume progression group (n=29): 23%
  - Plaque volume regression group (n=99): 77%

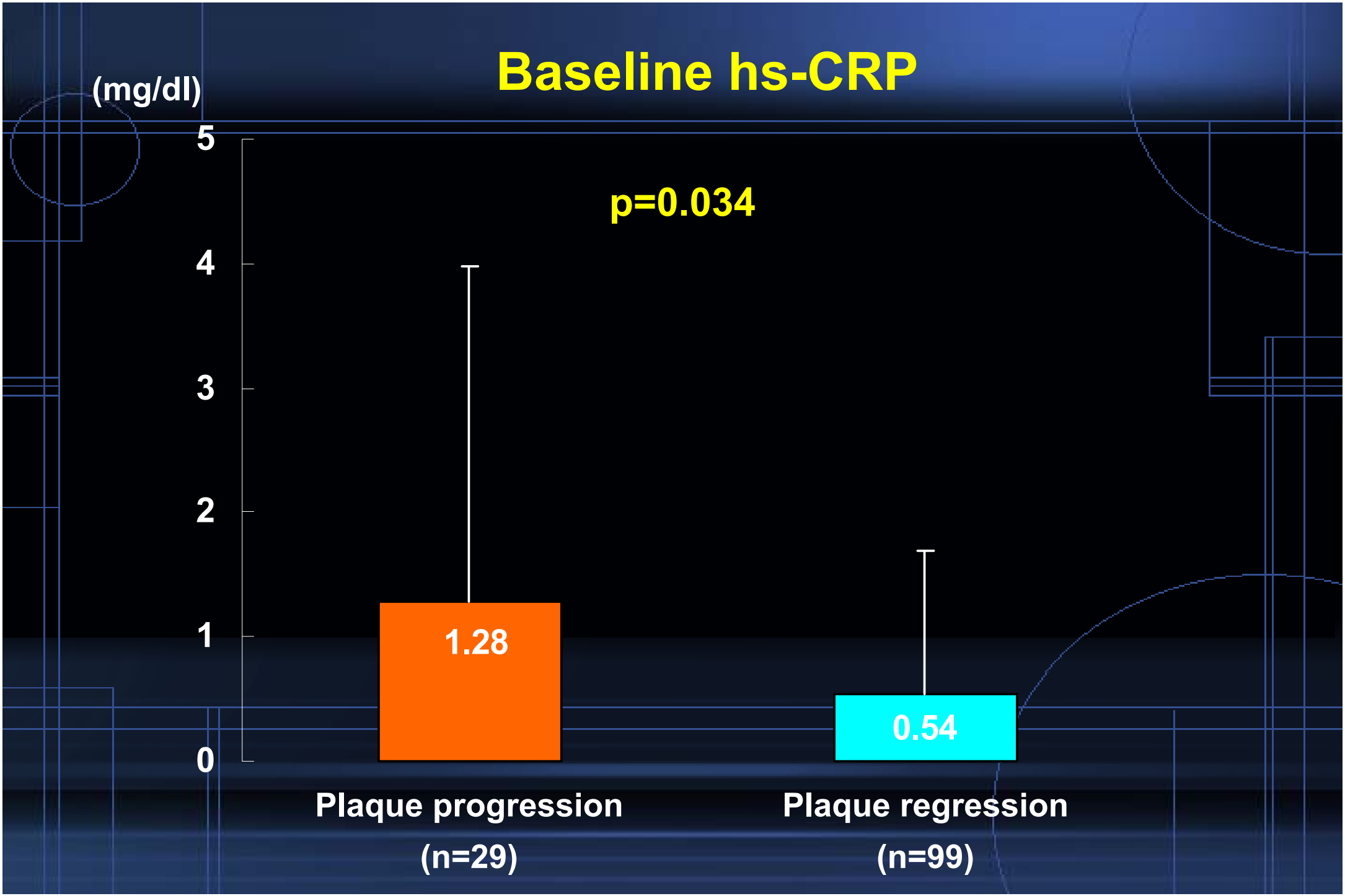
Follow-Up LDL-Cholesterol



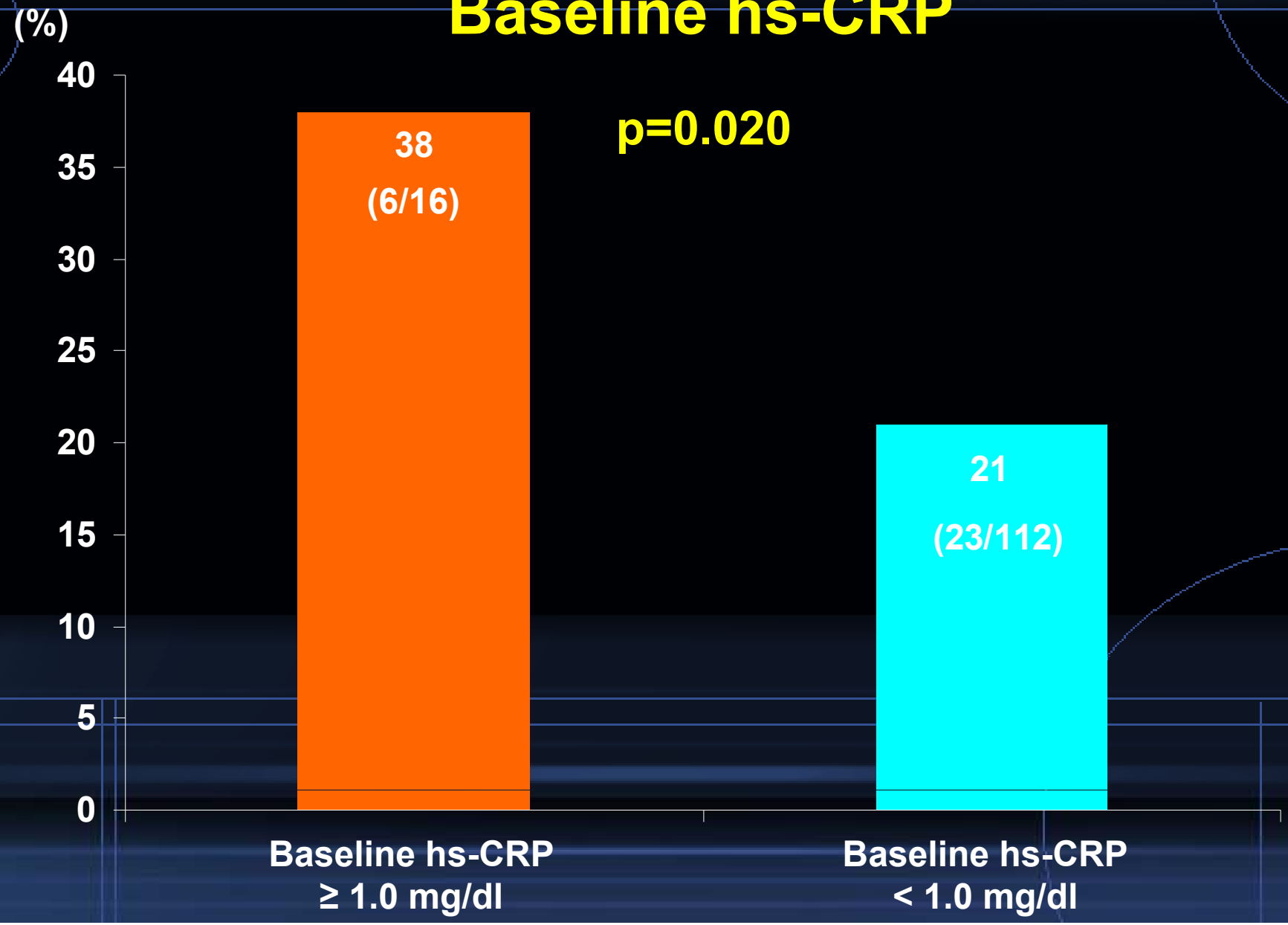
Plaque Progression According to Follow-Up LDL-Cholesterol



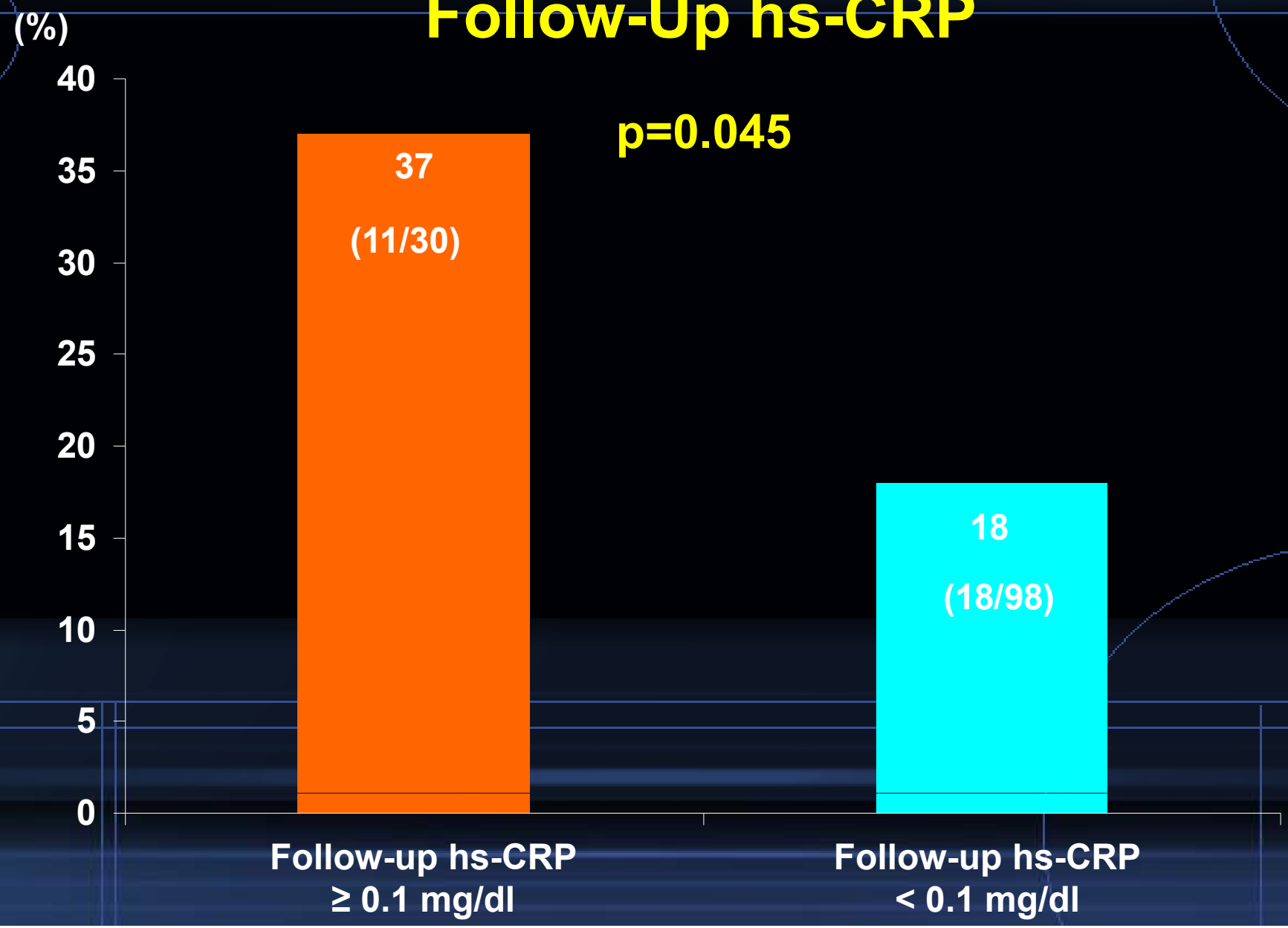
Baseline hs-CRP



Plaque Progression According to Baseline hs-CRP



Plaque Progression According to Follow-Up hs-CRP



Conclusion – Labroratory Findings vs. Plaque Progression by Statin

- In patients who use 20mg/day of rosuvastatin and 40mg/day of atorvastatin, follow-up LDL-C and baseline and follow-up hs-CRP are associated with plaque progression.

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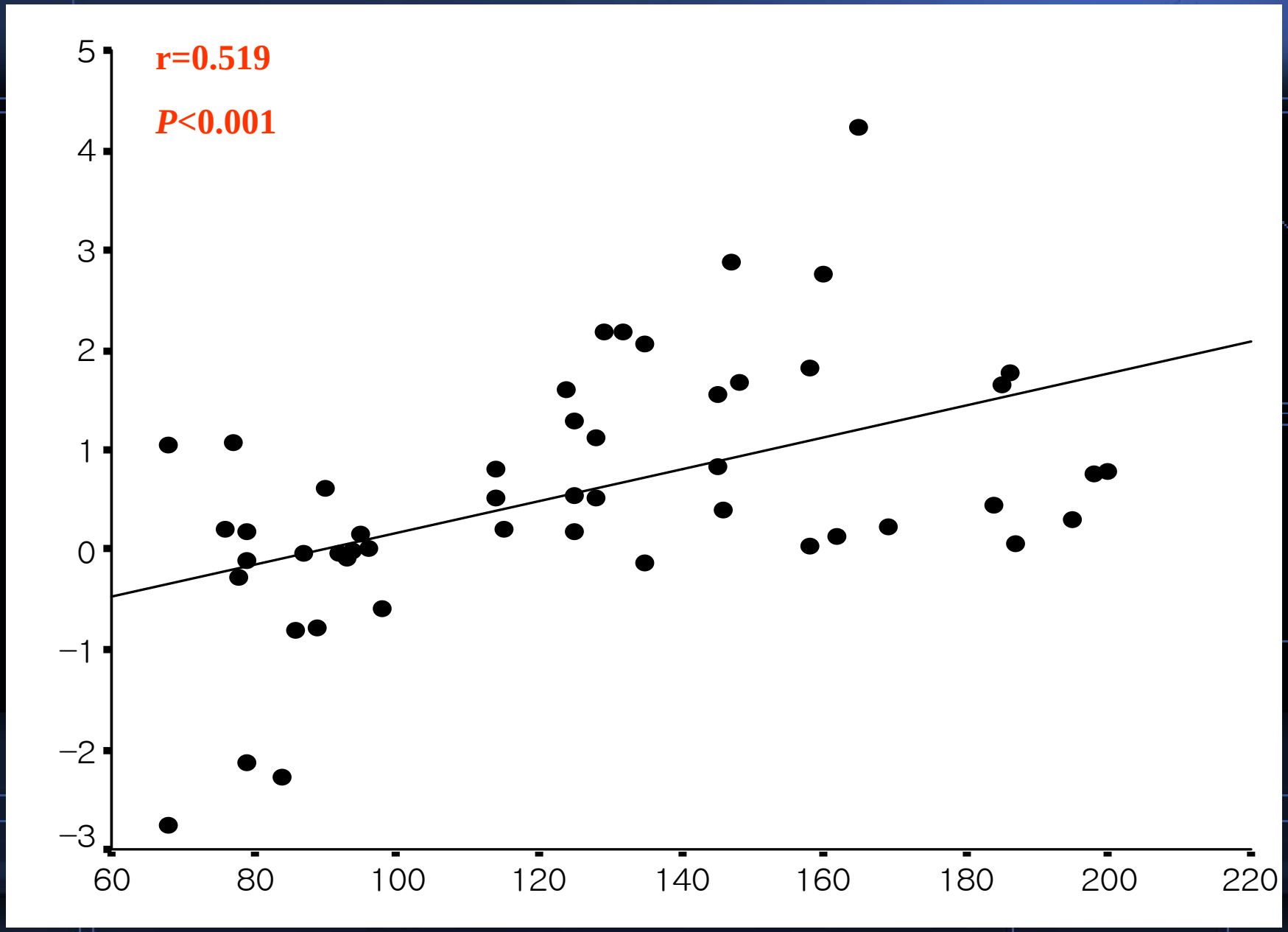
Disease Progression in Nonintervened Saphenous Vein Graft Segments

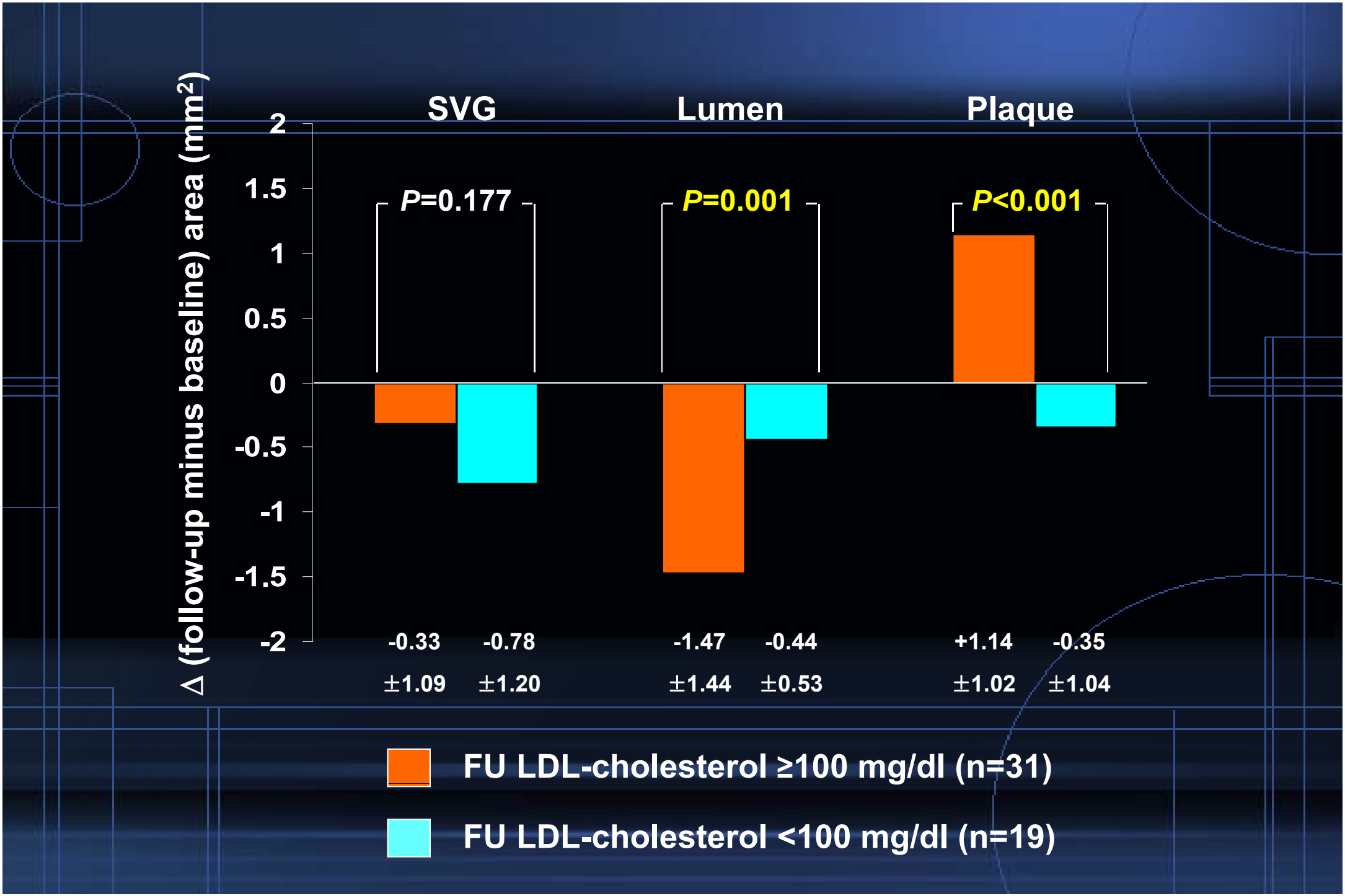
A Serial Intravascular Ultrasound Analysis

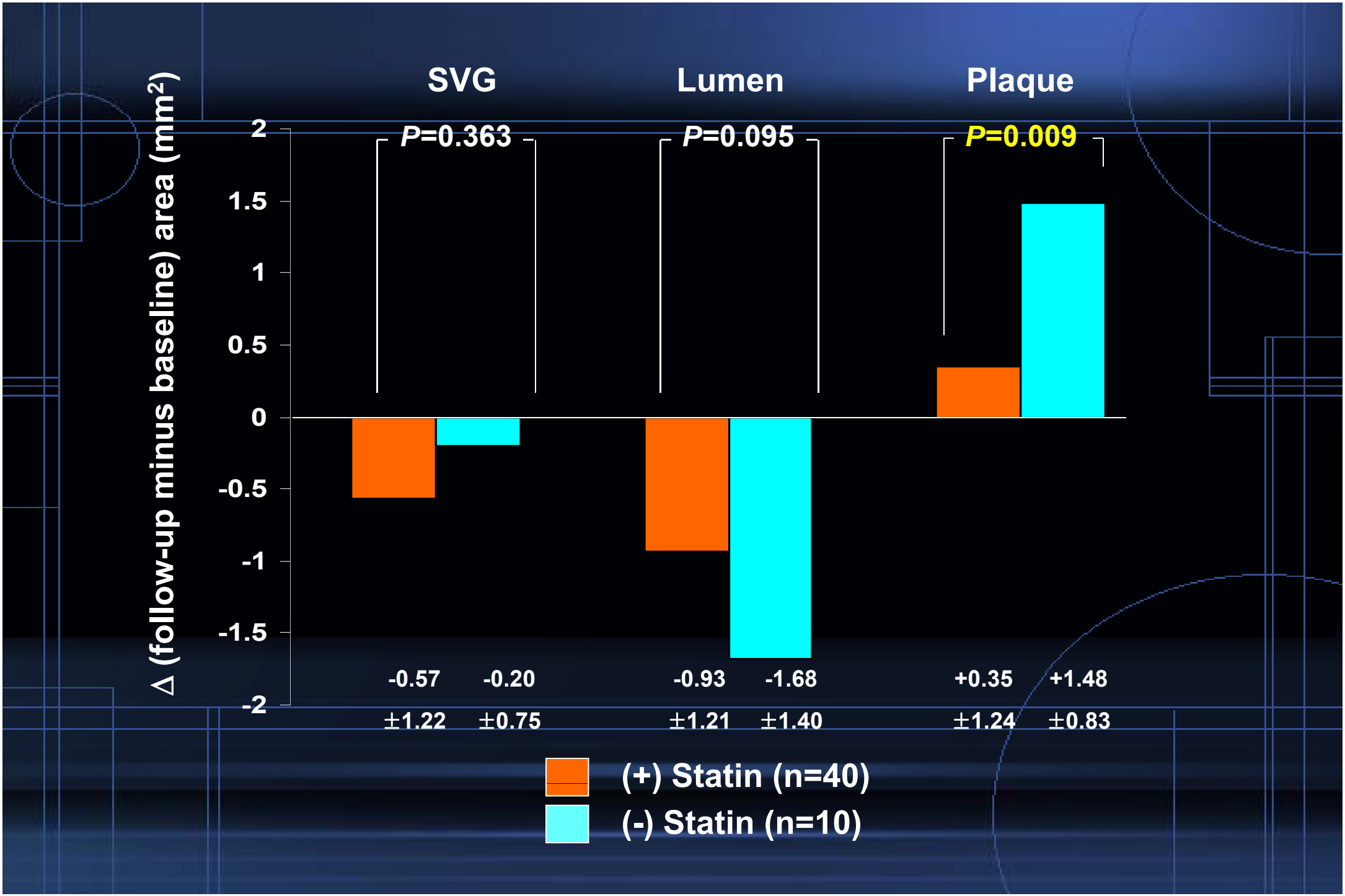
Young Joon Hong, MD,* Gary S. Mintz, MD,† Sang Wook Kim, MD,* Sung Yun Lee, MD,* Seok Yeon Kim, MD,* Teruo Okabe, MD,* Augusto D. Pichard, MD,* Lowell F. Satler, MD,* Ron Waksman, MD,* Kenneth M. Kent, MD, PHD,* William O. Suddath, MD,* Neil J. Weissman, MD*

Washington, DC; and New York

Hong YJ et al., J Am Coll Cardiol 2009;53:1257-1264


r=0.519
P<0.001
Δ Plaque area (mm²)
5
4
3
2
1
0
−1
−2
−3
60
80
100
120
140
160
180
200
220
Follow-up LDL-cholesterol (mg/dl)


SVG
Lumen
Plaque
Δ (follow-up minus baseline) area (mm²)
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
P=0.177
P=0.001
P<0.001
-0.33 ±1.09
-0.78 ±1.20
-1.47 ±1.44
-0.44 ±0.53
+1.14 ±1.02
-0.35 ±1.04
FU LDL-cholesterol ≥100 mg/dl (n=31)
FU LDL-cholesterol <100 mg/dl (n=19)


SVG
Lumen
Plaque
P=0.363
P=0.095
P=0.009
Δ (follow-up minus baseline) area (mm²)
2
1.5
1
0.5
0
-0.5
-1
-1.5
-2
-0.57 ±1.22
-0.20 ±0.75
-0.93 ±1.21
-1.68 ±1.40
+0.35 ±1.24
+1.48 ±0.83
(+) Statin (n=40)
(-) Statin (n=10)

Conclusion - SVG

- **Lumen loss in non-intervened SVG segments correlated with an increase in plaque area and a decrease in SVG area (plaque growth and negative remodeling) with a linear relationship between plaque growth vs. follow-up LDL-cholesterol leading to long-term lumen loss.**

Baseline Plaque Components vs. on Plaque Progression in Patients with Angina Pectoris Who Uses Usual Dose of Rosuvastatin

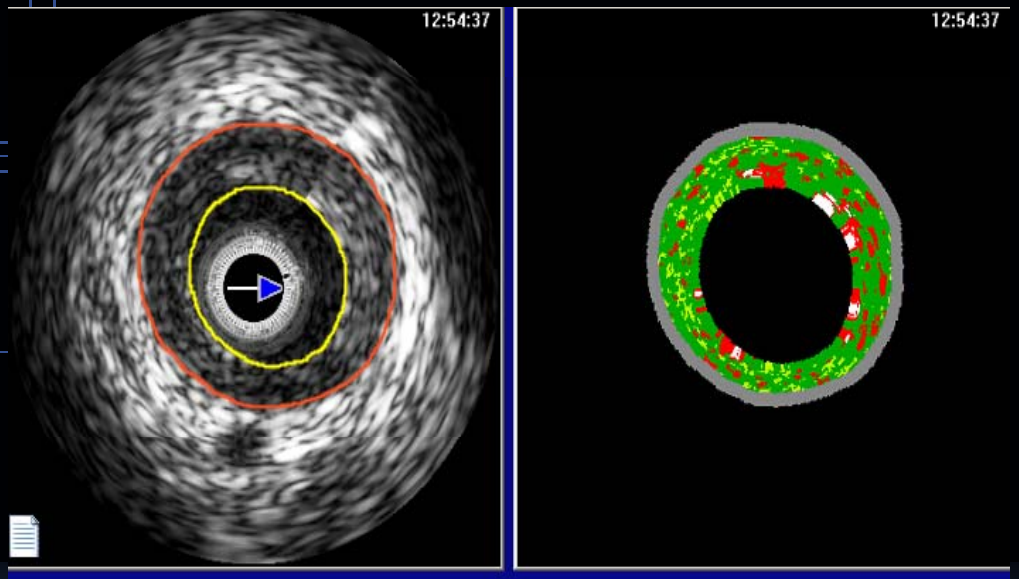
- 66 patients who underwent baseline and 9-month follow-up VH-IVUS for non-intervened intermediate coronary stenosis
- Patients with angina pectoris who used **10 mg/d of rosuvastatin**
- At the baseline minimum lumen area (MLA) site

  - Plaque progression group (n=22)

  - Plaque regression group (n=44)

Plaque Progression at 9-Month Follow-Up

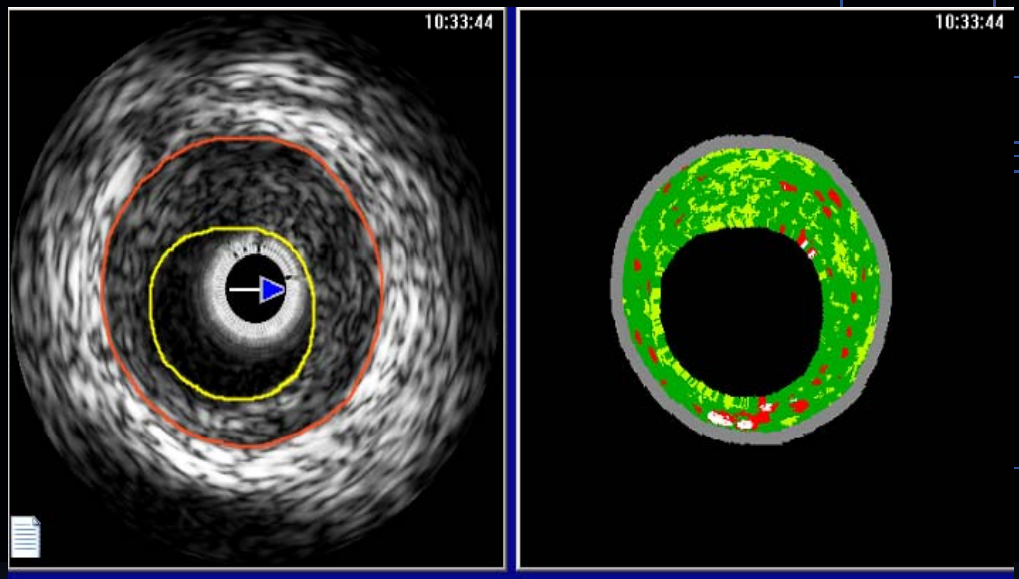
Baseline



Lumen Area	8.1 mm	
Vessel Area	21.7 mm	
Plaque Area	13.6 mm	
% Plaque Burden	63 %	
FI Green Area	7.0 mm	71 %
FF Light Green Area	0.9 mm	9 %
DC White Area	0.3 mm	3 %
NC Red Area	1.6 mm	17 %

More ...

Follow-up

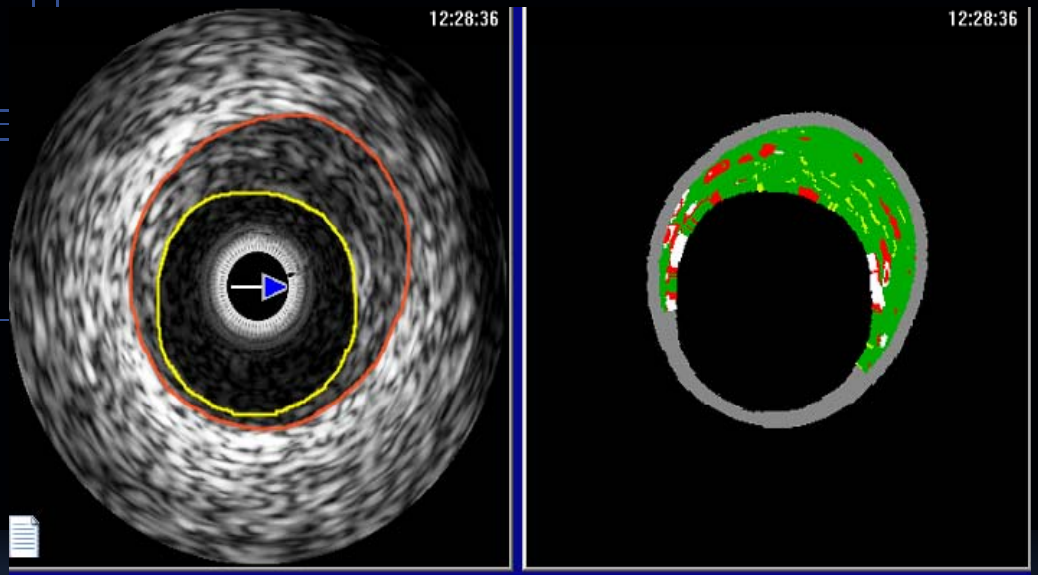


Lumen Area	8.5 mm	
Vessel Area	25.7 mm	
Plaque Area	17.2 mm	
% Plaque Burden	67 %	
FI Green Area	9.7 mm	75 %
FF Light Green Area	2.4 mm	18 %
DC White Area	0.2 mm	1 %
NC Red Area	0.8 mm	6 %

More ...

Plaque Regression at 9-Month Follow-Up

Baseline



Lumen Area	13.1 mm	
Vessel Area	25.3 mm	
Plaque Area	12.2 mm	
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FI Green Area	6.1 mm	80 %
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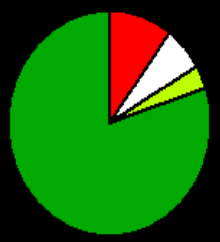
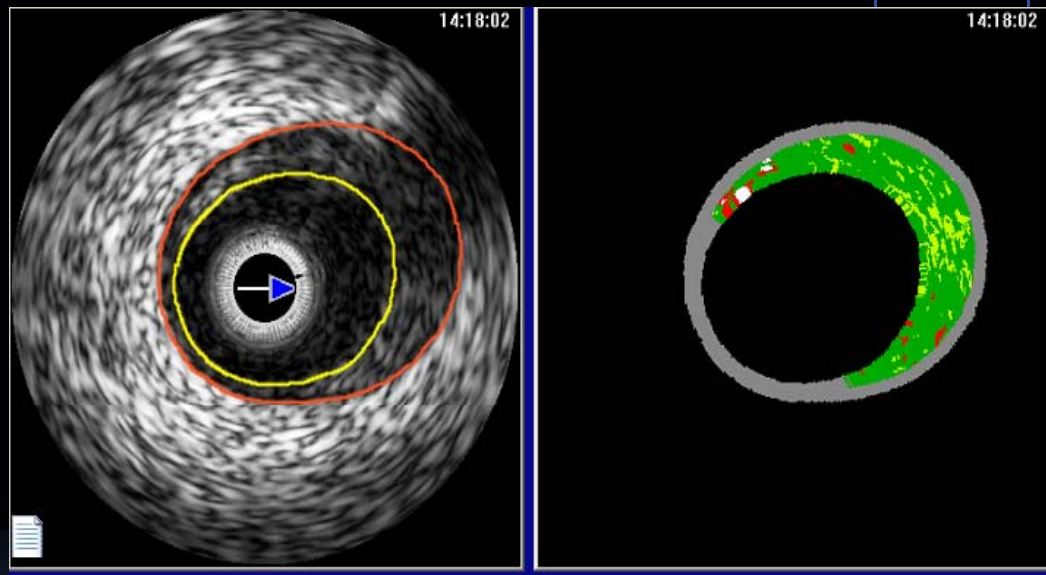
More ...



Follow-up



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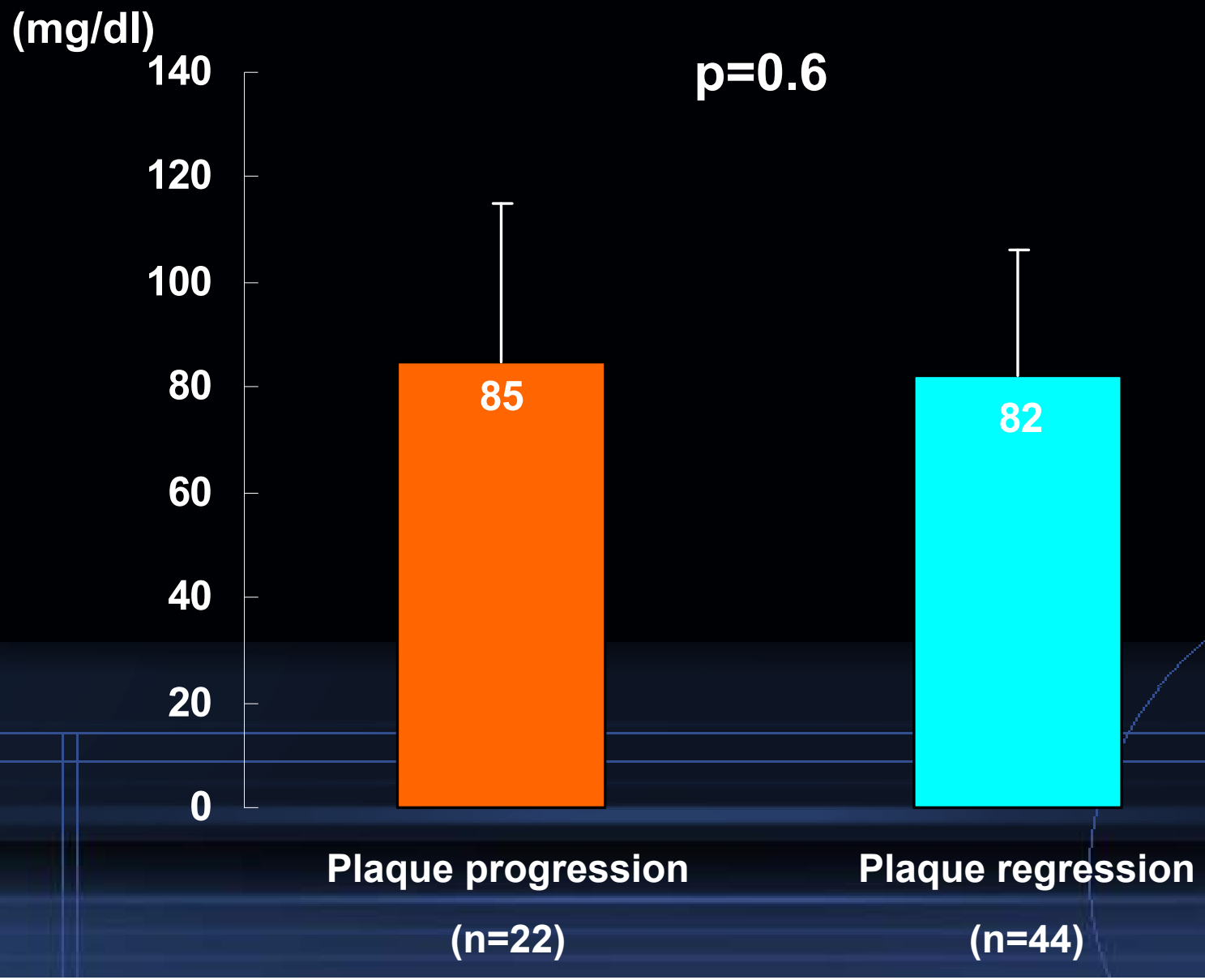
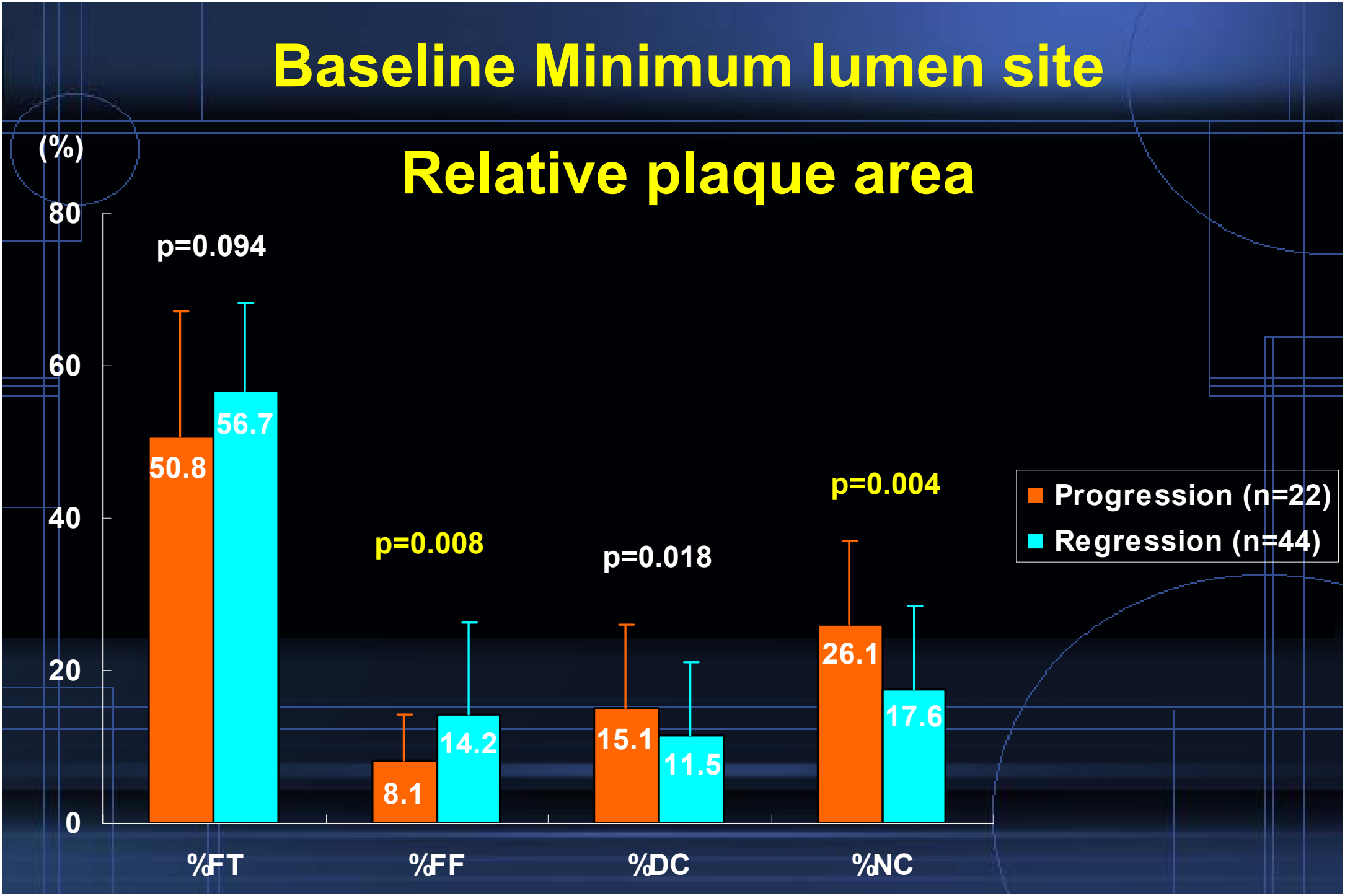
More ...

9-Month Follow-Up LDL-Cholesterol

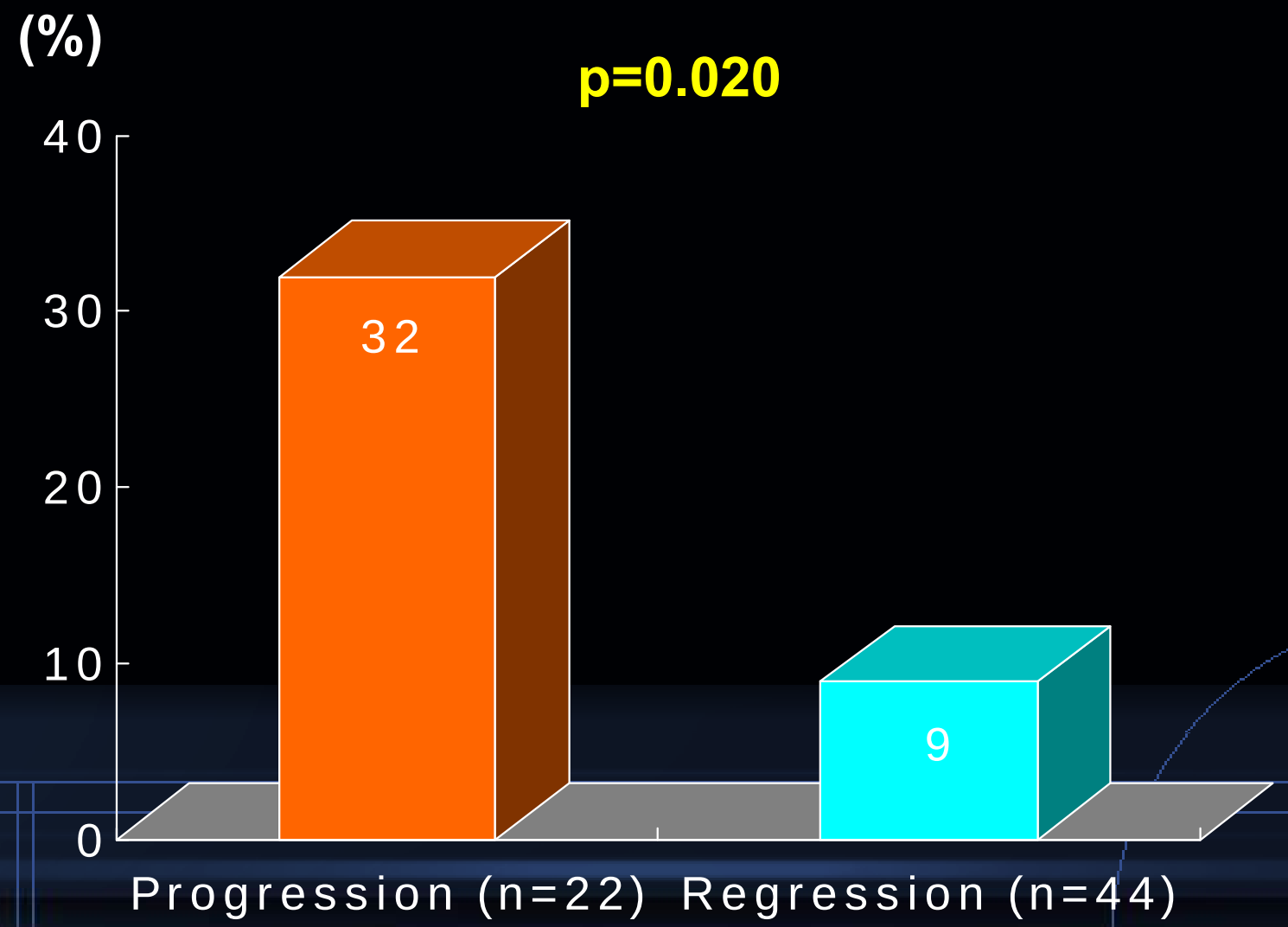


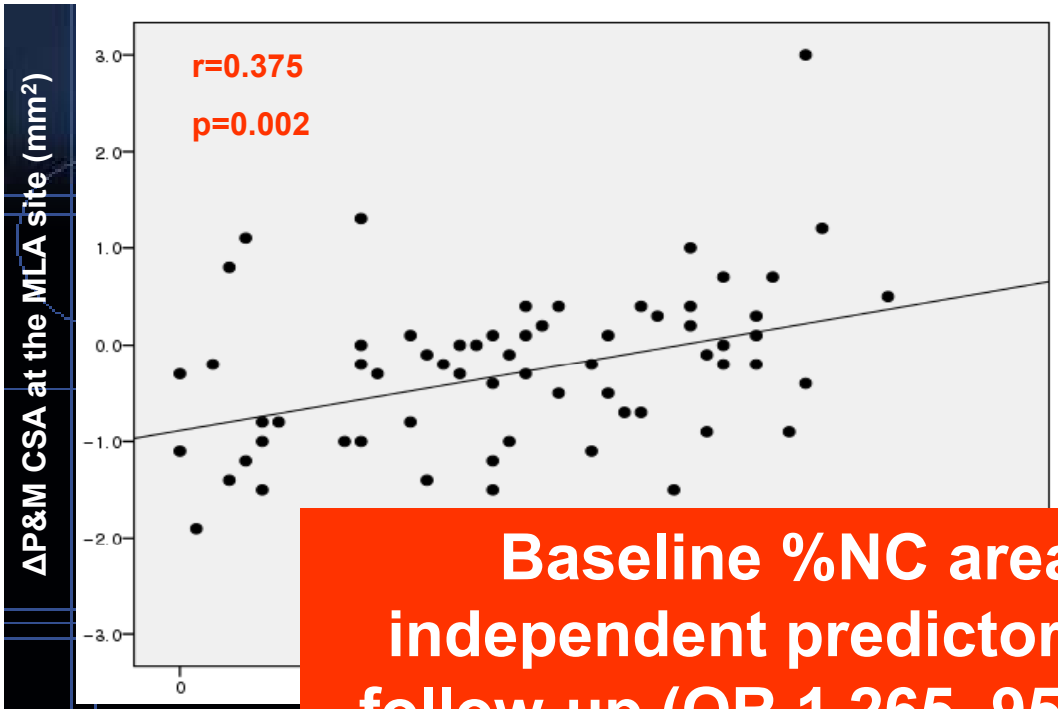
Baseline Minimum lumen site

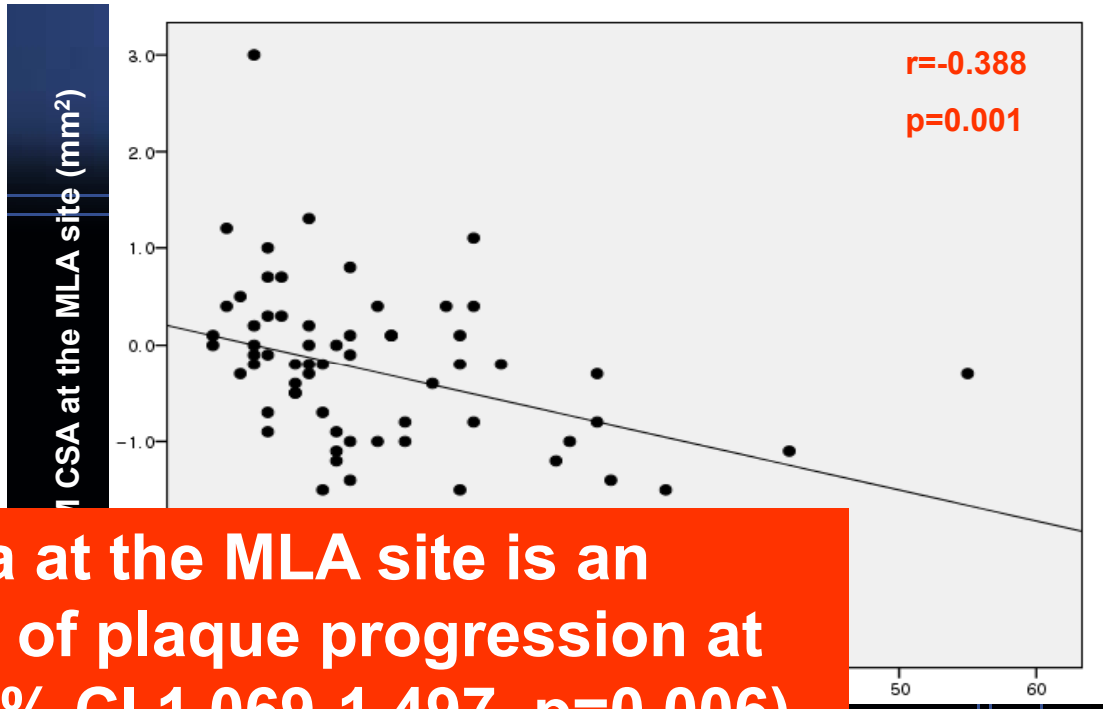
Relative plaque area



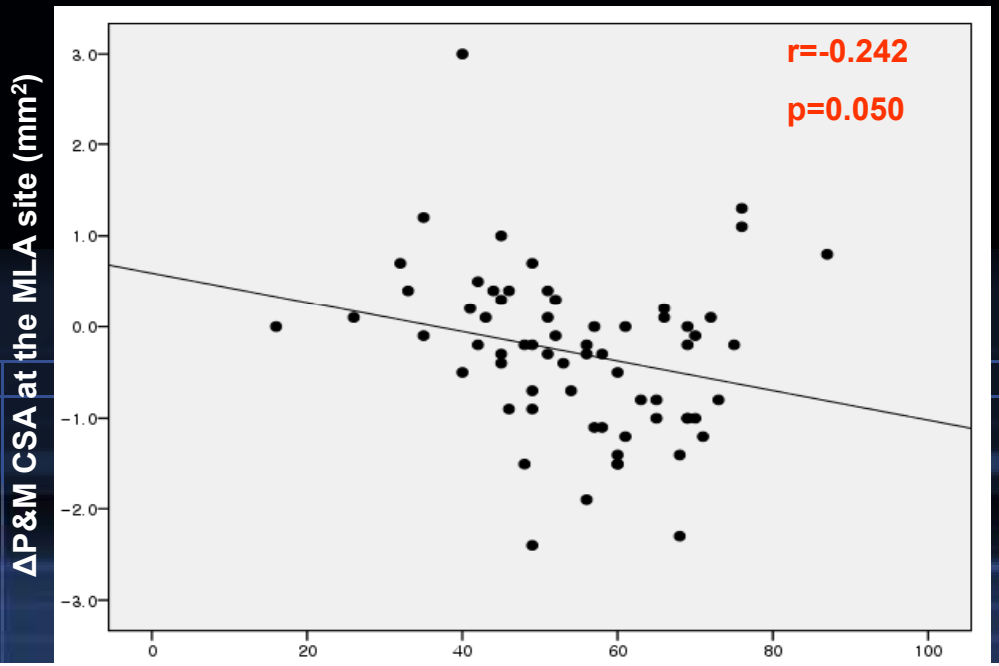
Baseline Thin-Cap Fibroatheroma







Baseline %NC area at the MLA site is an independent predictor of plaque progression at follow-up (OR 1.265, 95% CI 1.069-1.497, p=0.006)



Baseline %FT area at the MLA site (%)

Conclusion – Plaque Components vs. Plaque Progression

- **In patients with angina pectoris who uses usual dose of rosuvastatin and reaches follow-up LDL-cholesterol around 80 mg/dl, baseline NC component is associated with plaque progression.**

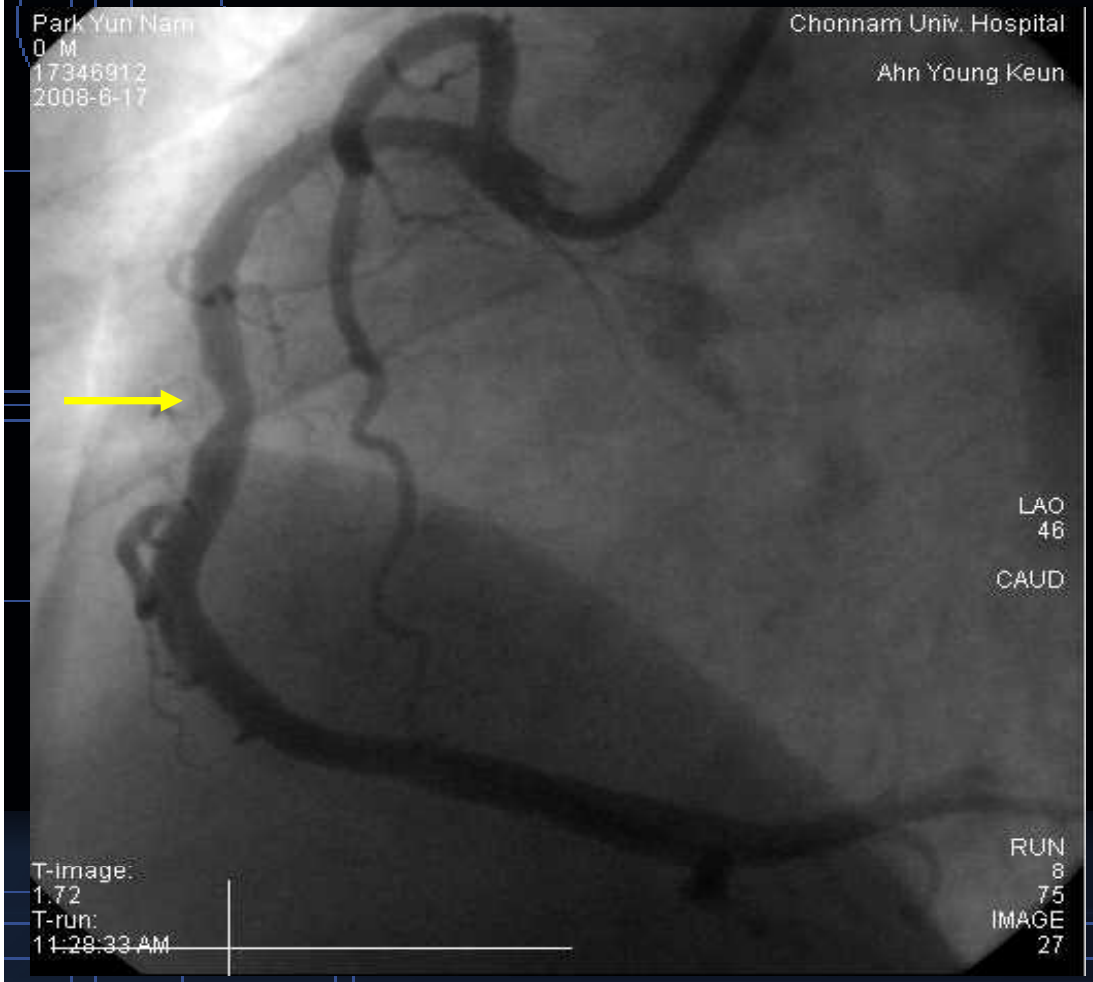
Livalo® (Pitavastatin) in Acute Myocardial Infarction Study (LAMIS)

IVUS and VH-IVUS analysis in LAMIS (n=50)

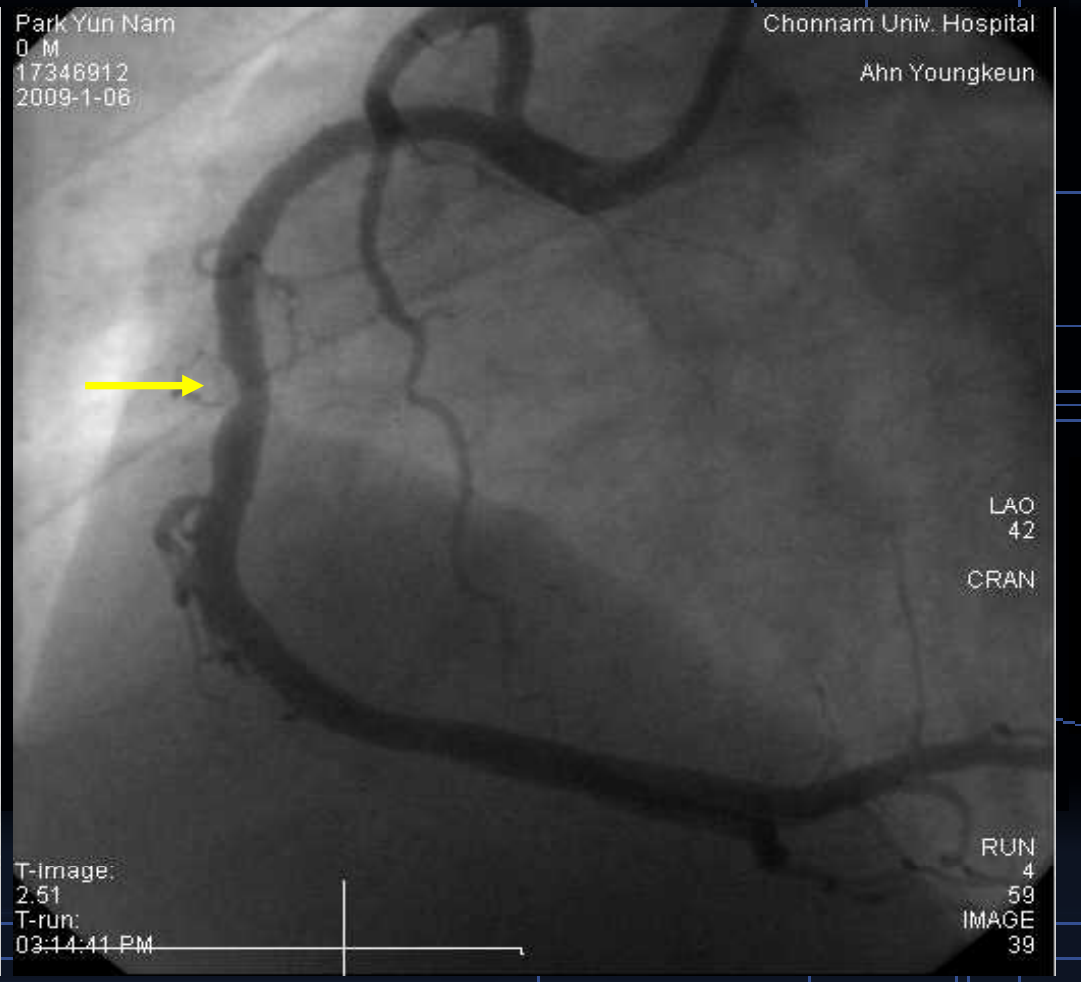
Pitavastatin 2mg / day

Non-culprit, Non-intervened segments

Baseline

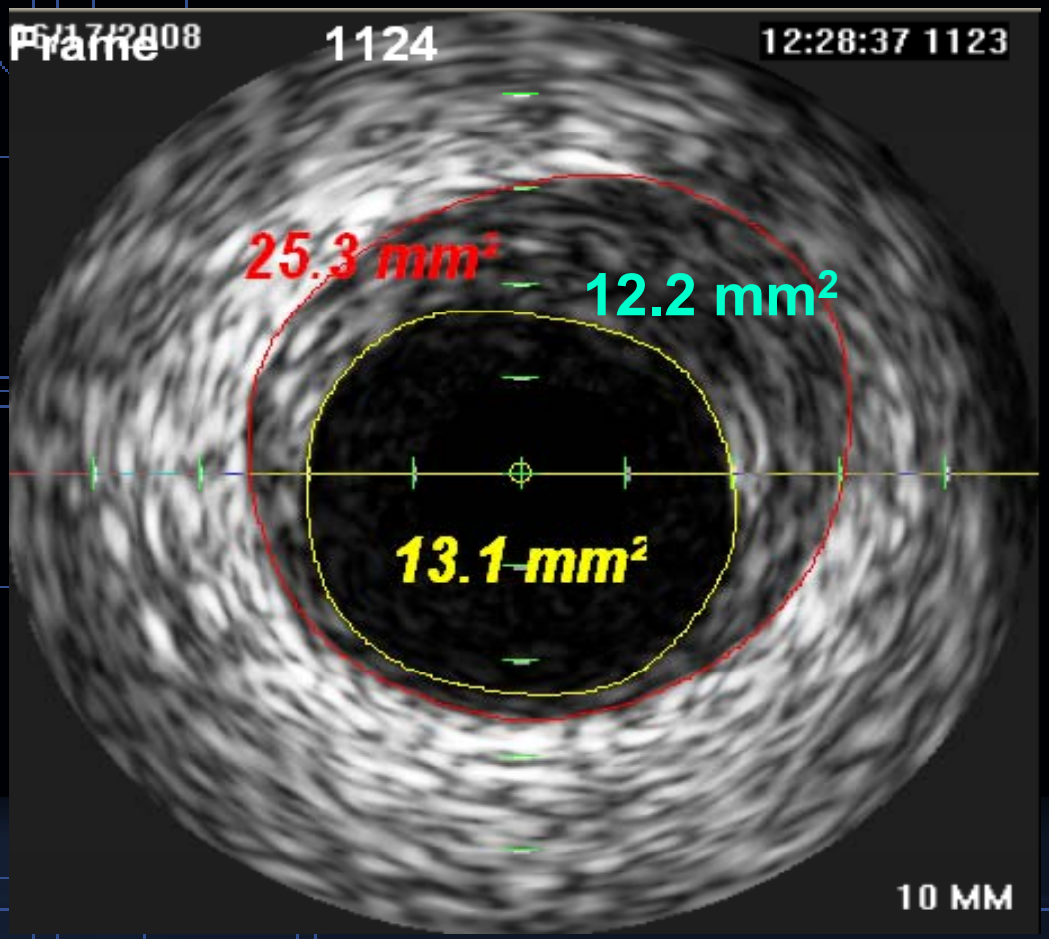


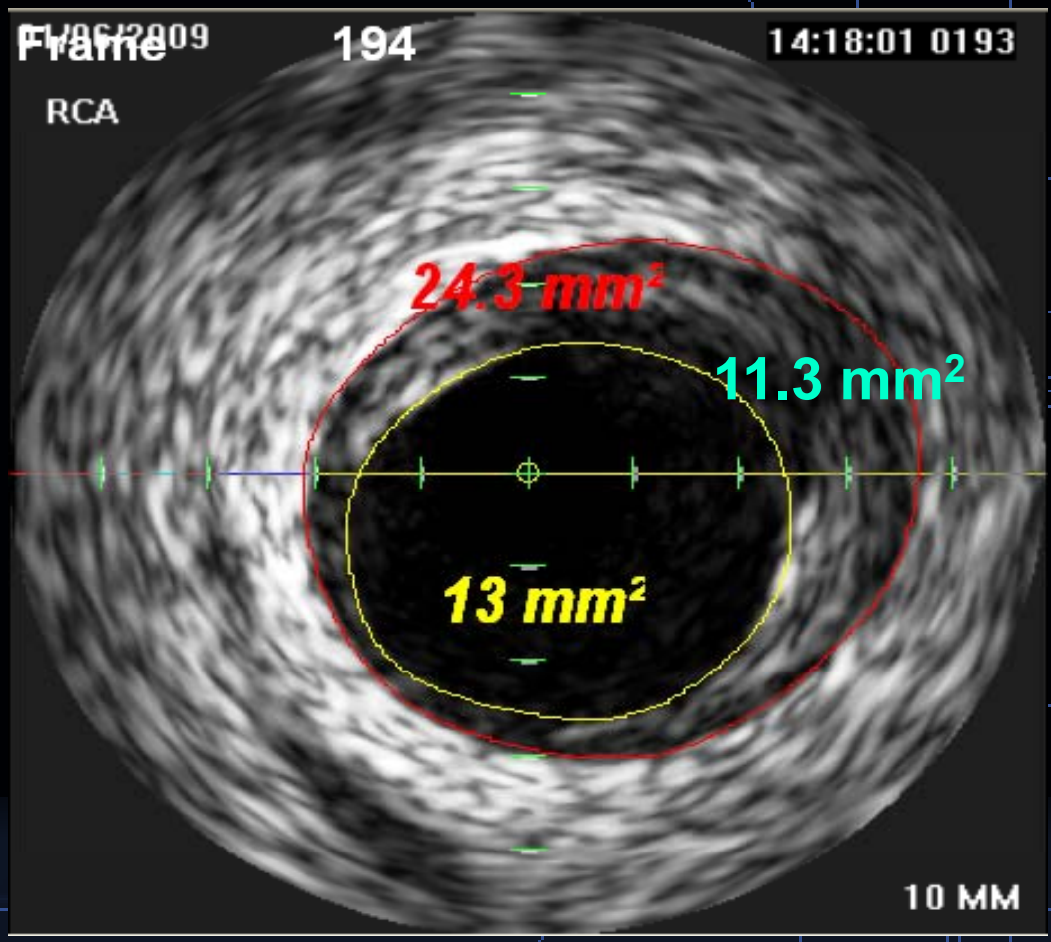
Follow up



Baseline

Follow up

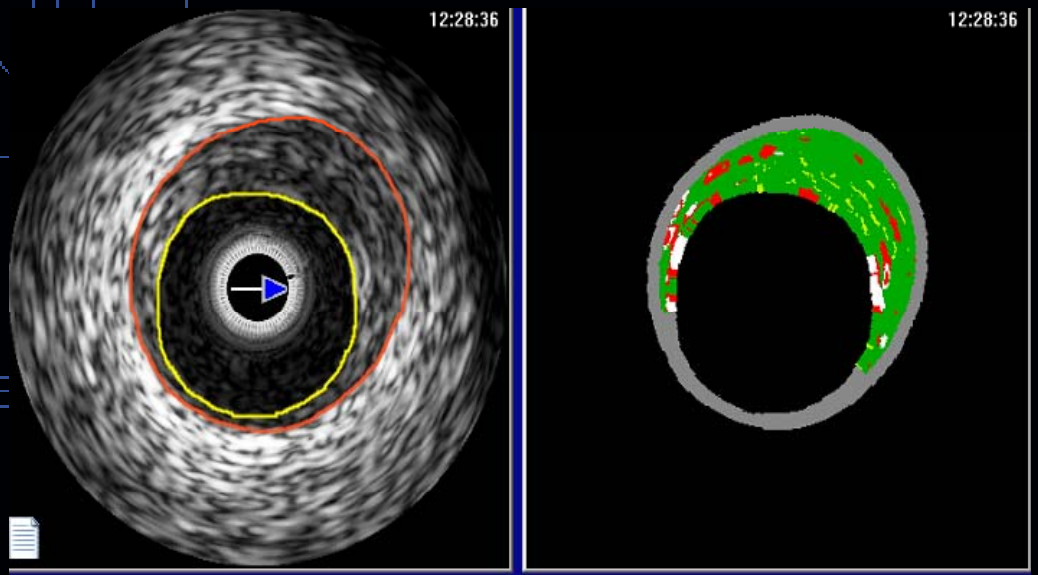




Plaque burden 48%

Plaque burden 46%

Baseline



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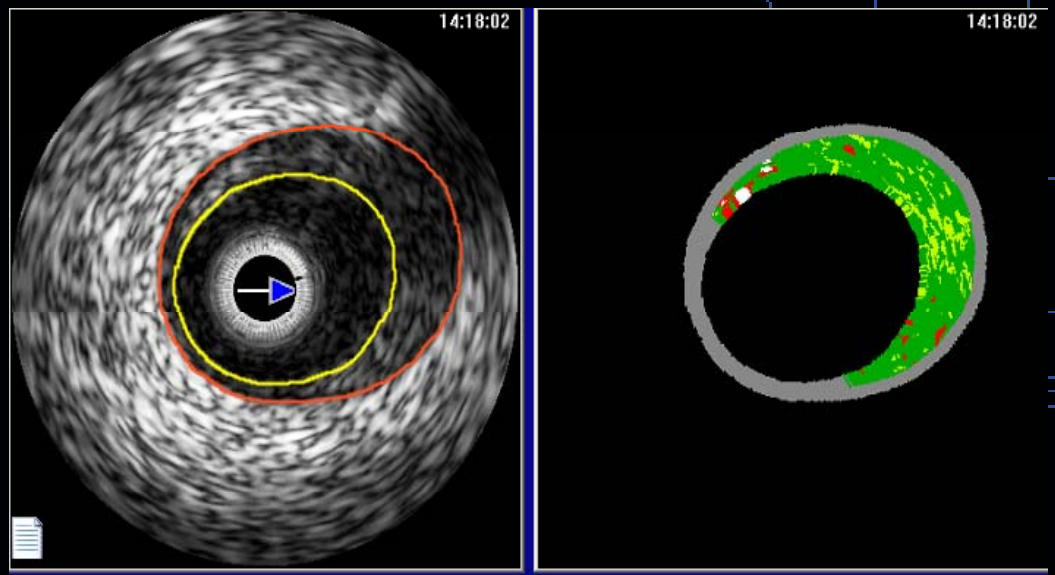
Follow up



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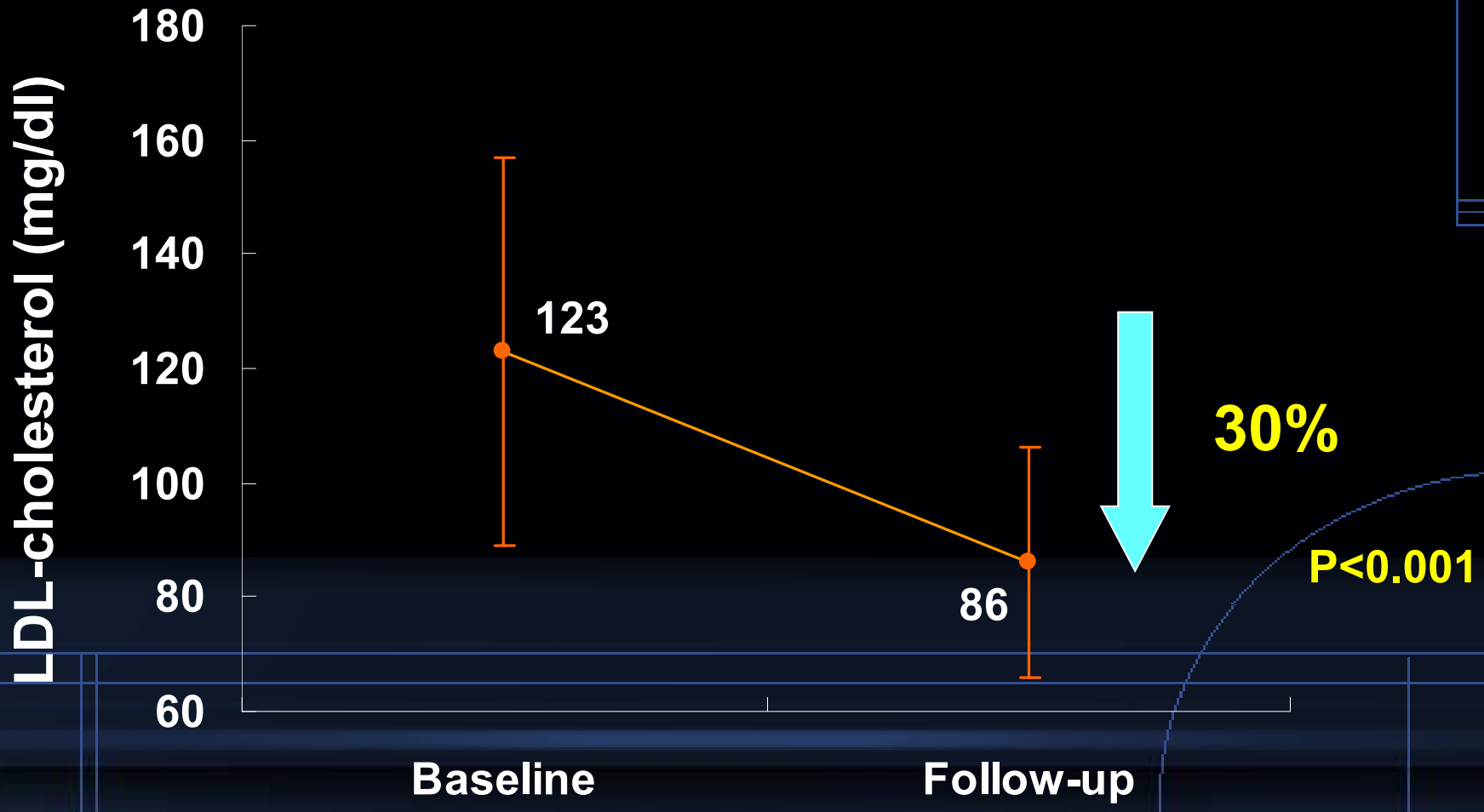
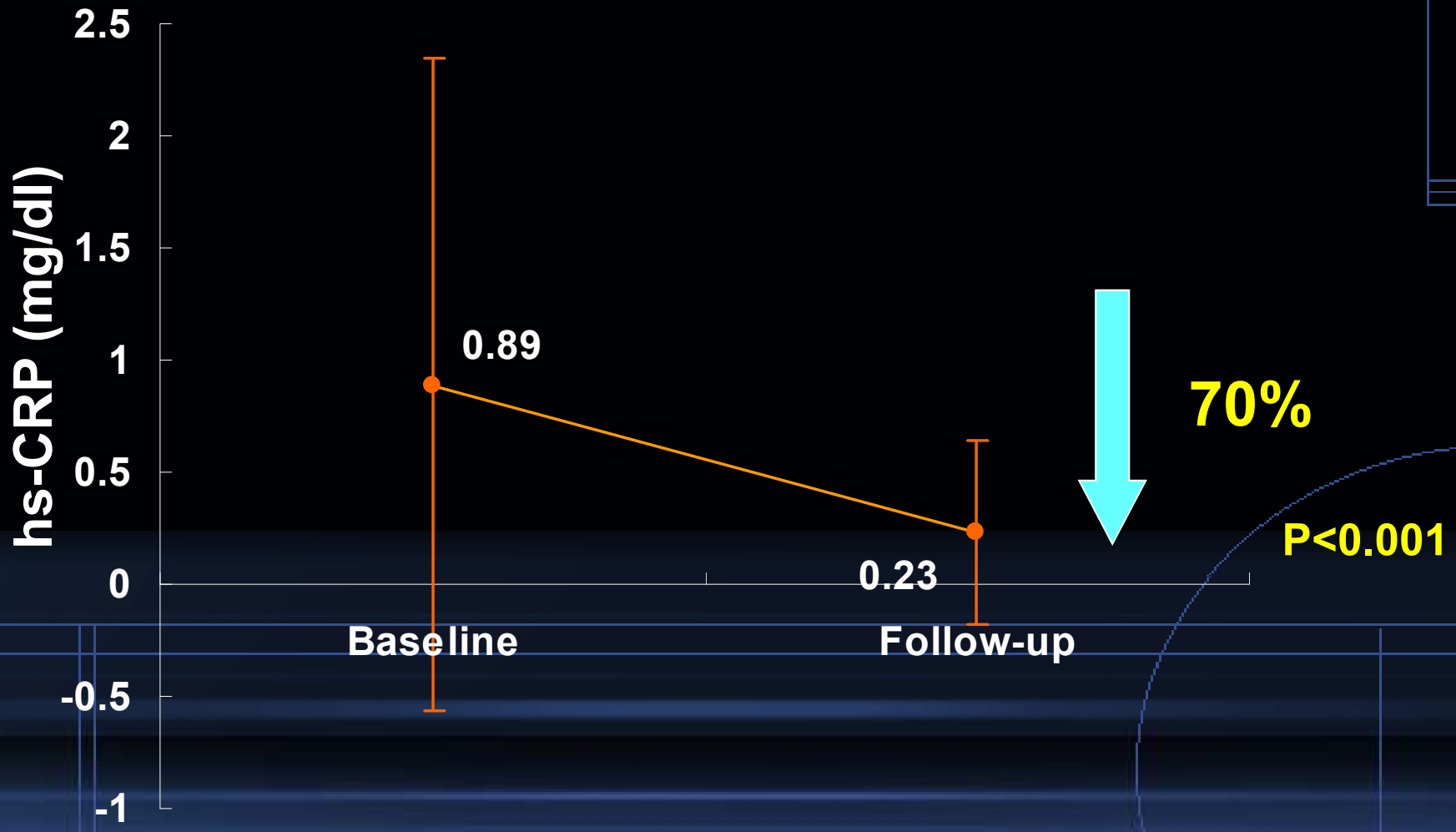
More ...

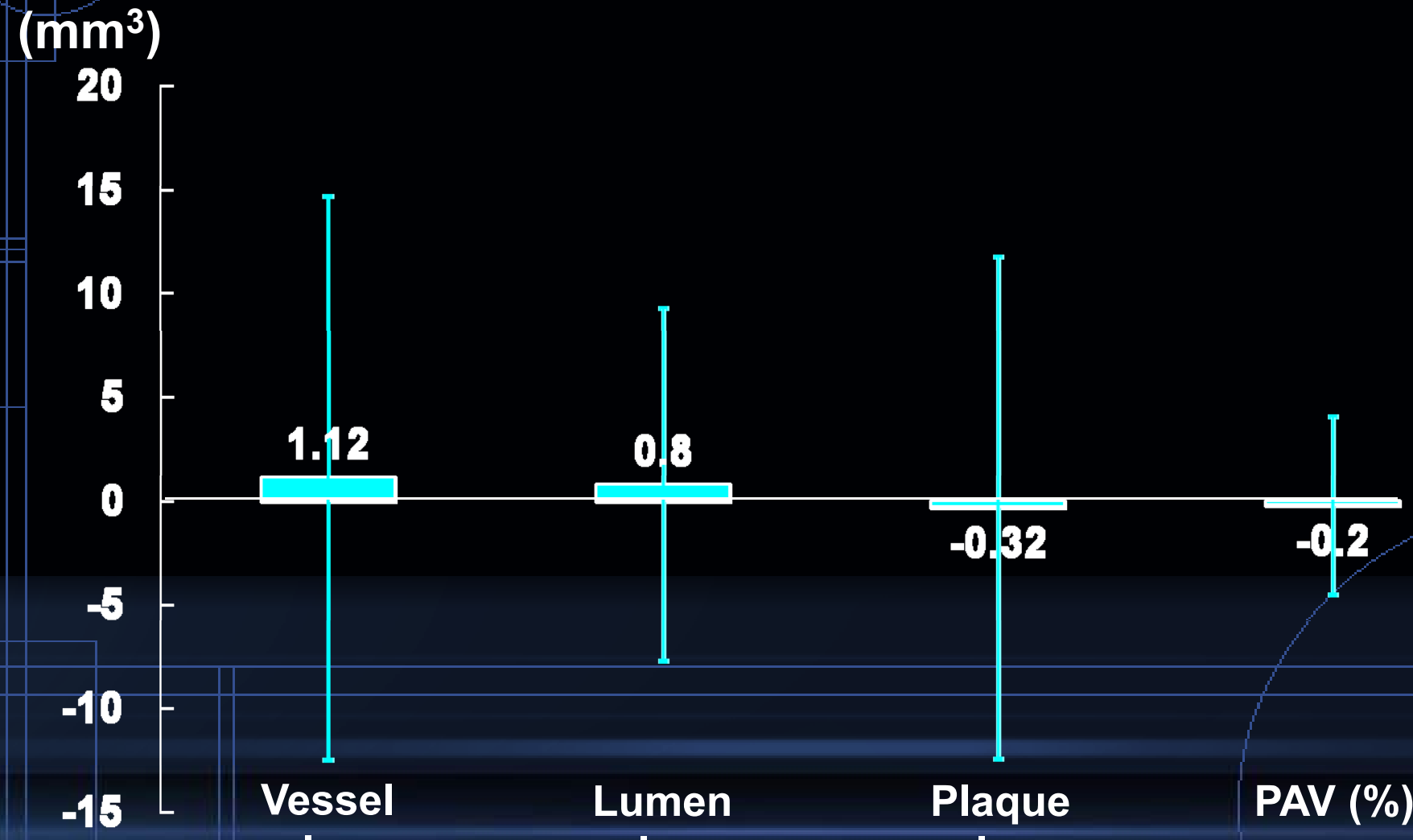
Change of LDL-Cholesterol From Baseline to FU (Mean 7.7 Months)



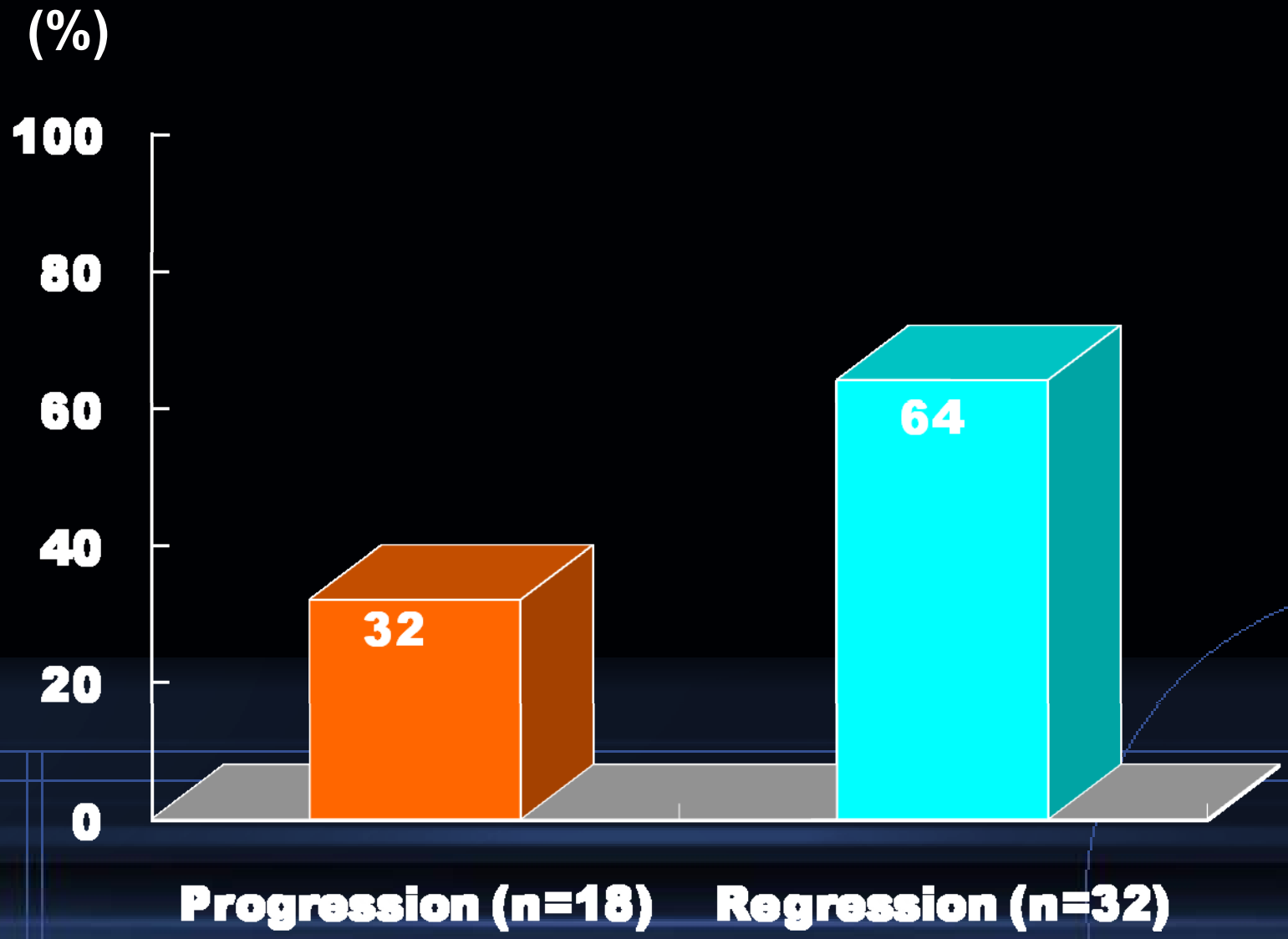
Change of hs-CRP From Baseline to FU (Mean 7.7 Months)



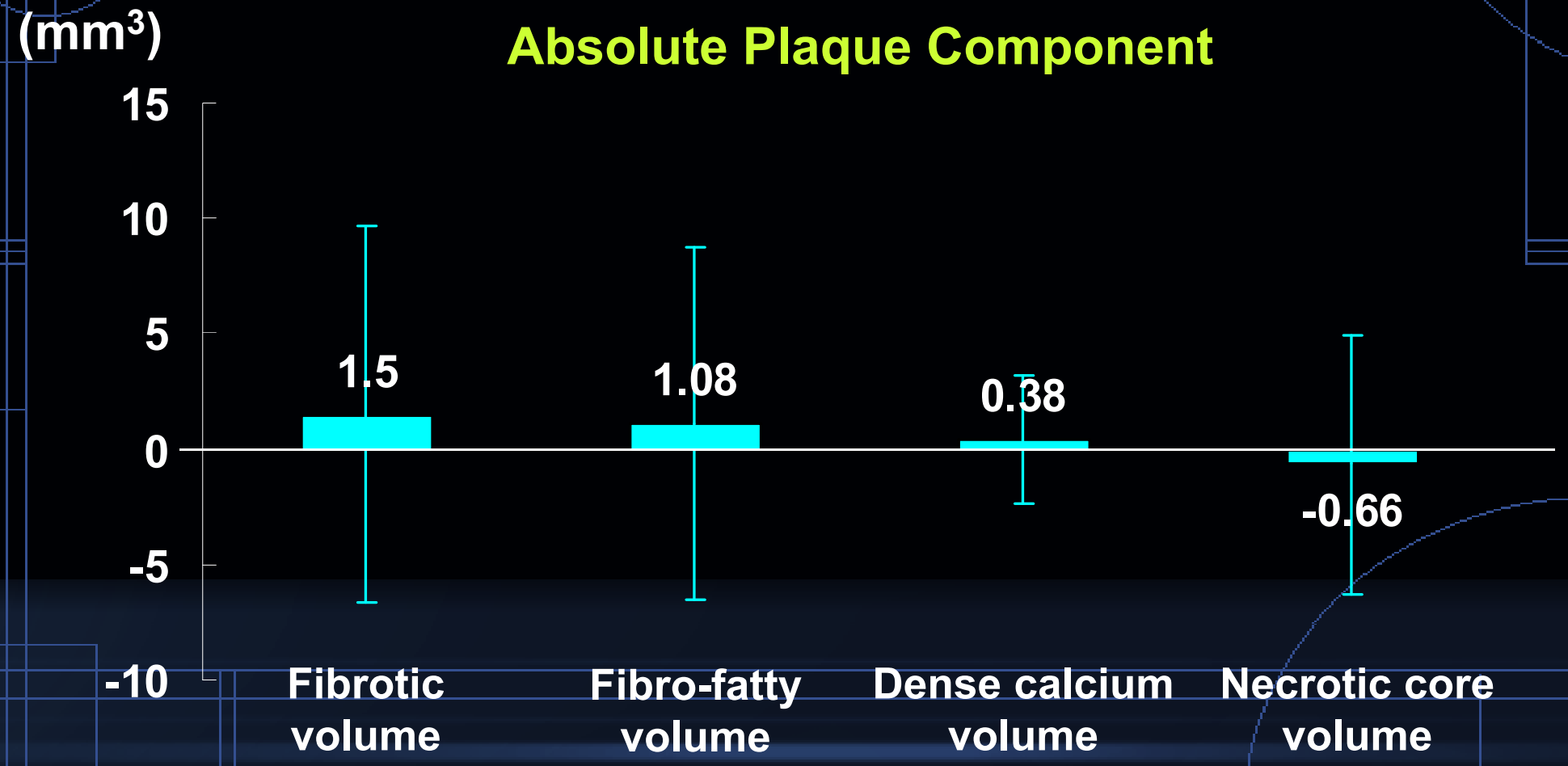
Changes of Grey-Scale IVUS Parameters From Baseline to FU (Mean 7.7 Months)



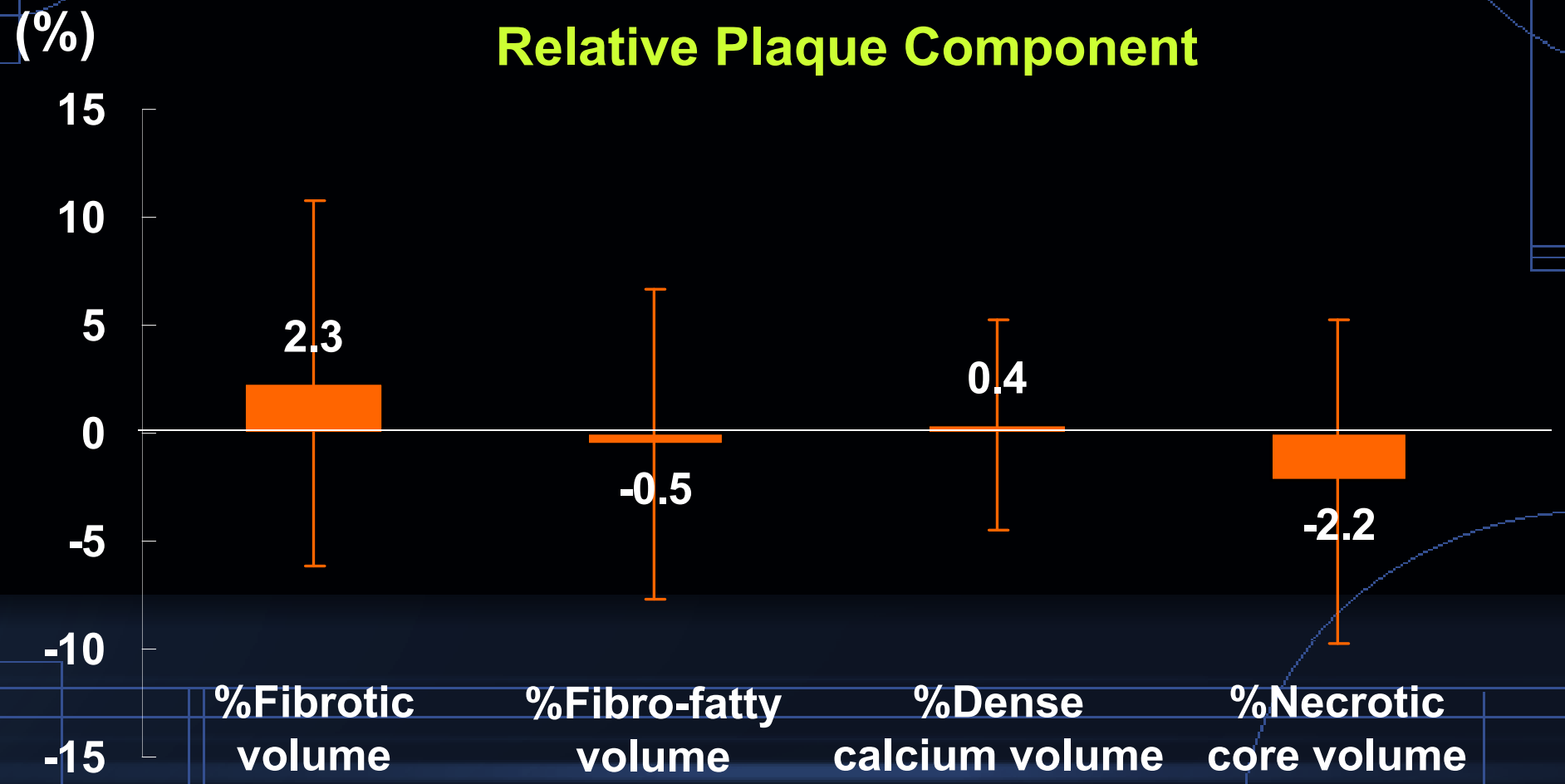
Plaque Progression/Regression at FU



Changes of VH-IVUS Parameters From Baseline to FU (Mean 7.7 Months)

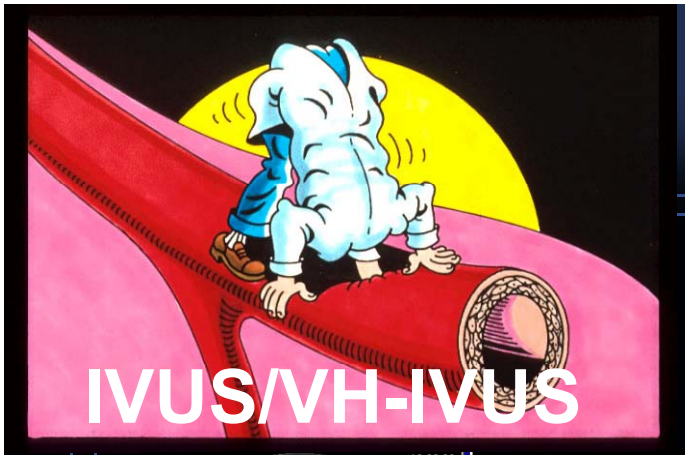


Changes of VH-IVUS Parameters From Baseline to FU (Mean 7.7 Months)

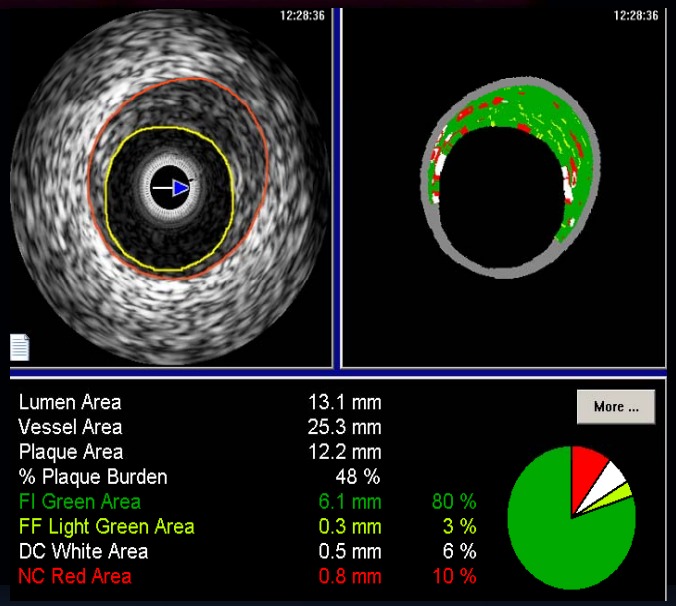


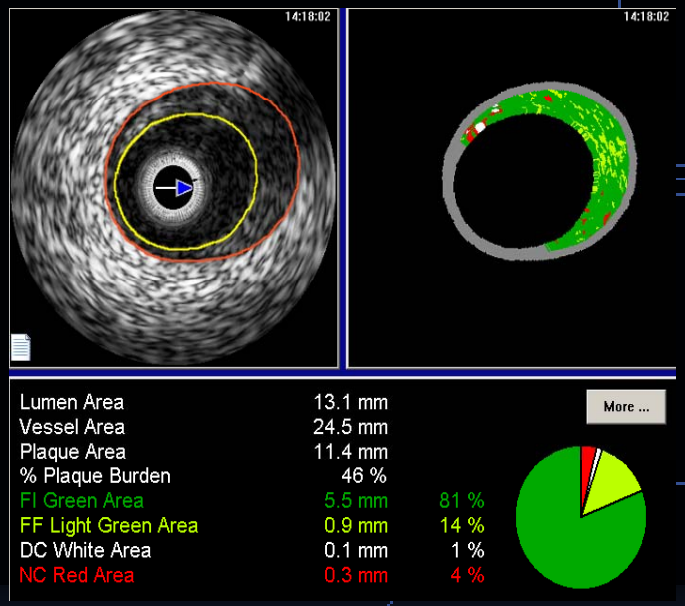
Conclusion – IVUS Study in LAMIS

- **Usual dose of pitavastatin (2mg/day) decreased LDL-C and CRP levels effectively**
- **It had some effect on plaque regression and compositional change in non-culprit, non-intervened segments in AMI patients.**
- **With more intensive dose of statin, plaque regression and plaque compositional change probably could be more rapidly achieved.**



Intensive lipid-lowering therapy





Clinical Event

Future Perspectives in LAMIS

- More long-term follow-up data
- High dose Livalo (4mg)
- More IVUS and VH-IVUS follow-up data
  -- Plaque regression
  -- Plaque compositional change
- Other imaging modality: OCT, CT, MR…

Thank You For Your Attention!

LAMIS Group