

# Atherosclerosis Regression

An Overview of Recent Findings & Issues

13th  
Angioplasty  
Summit 2008

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# Atherosclerosis

Progression 

## Reversibility of Arterial Lesions

**Animal models:**

documented in a wide range of species

**Humans:**

There are growing evidences of plaque regression in mild atherosclerotic disease

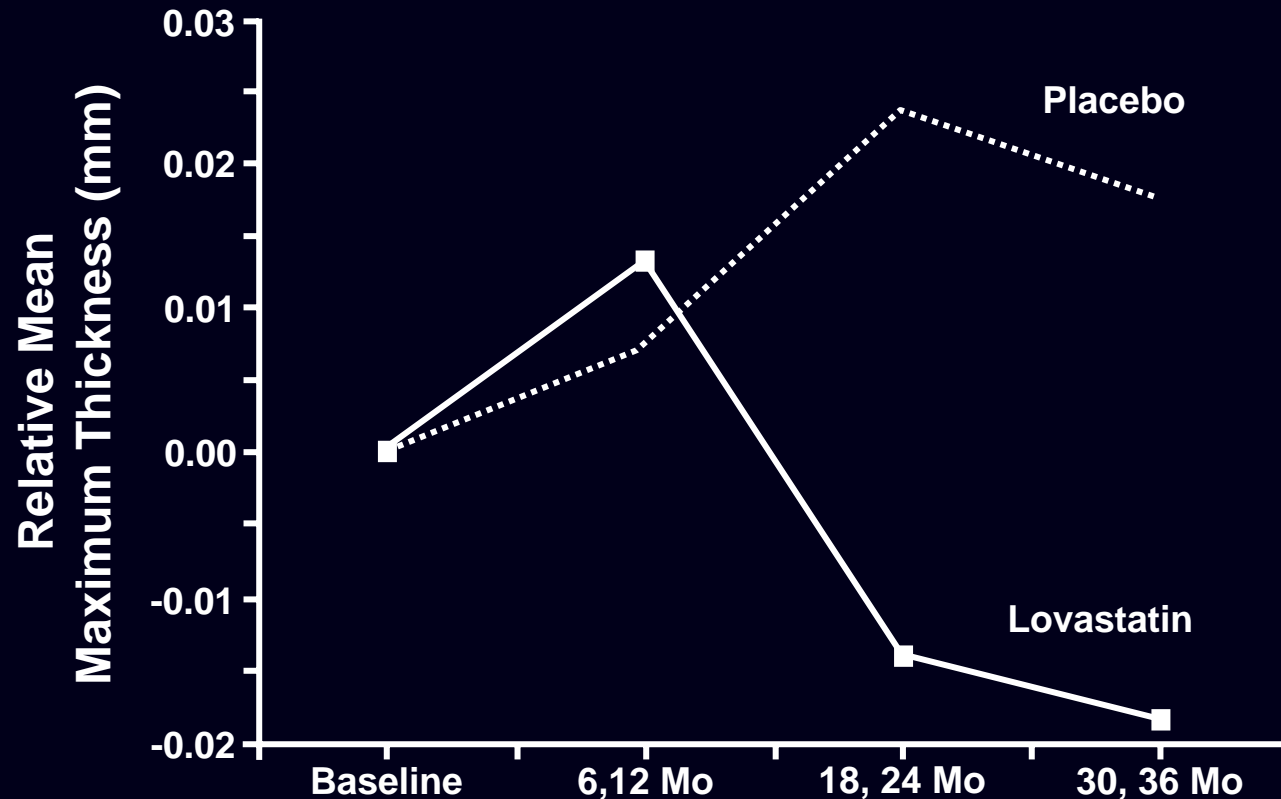
\* Atherosclerosis is usually viewed as a chronic progressive disease characterized by continuous accumulation of atheroma within the arterial wall.

# Presentation

- Evidences of plaque regression
- Predictors of plaque regression
- Clinical significance of regression
- Future perspective

Evidences of  
Plaque Regression  
Carotid Artery

# Effect of Lovastatin on Early Carotid Atherosclerosis & CV Events: ACAPS



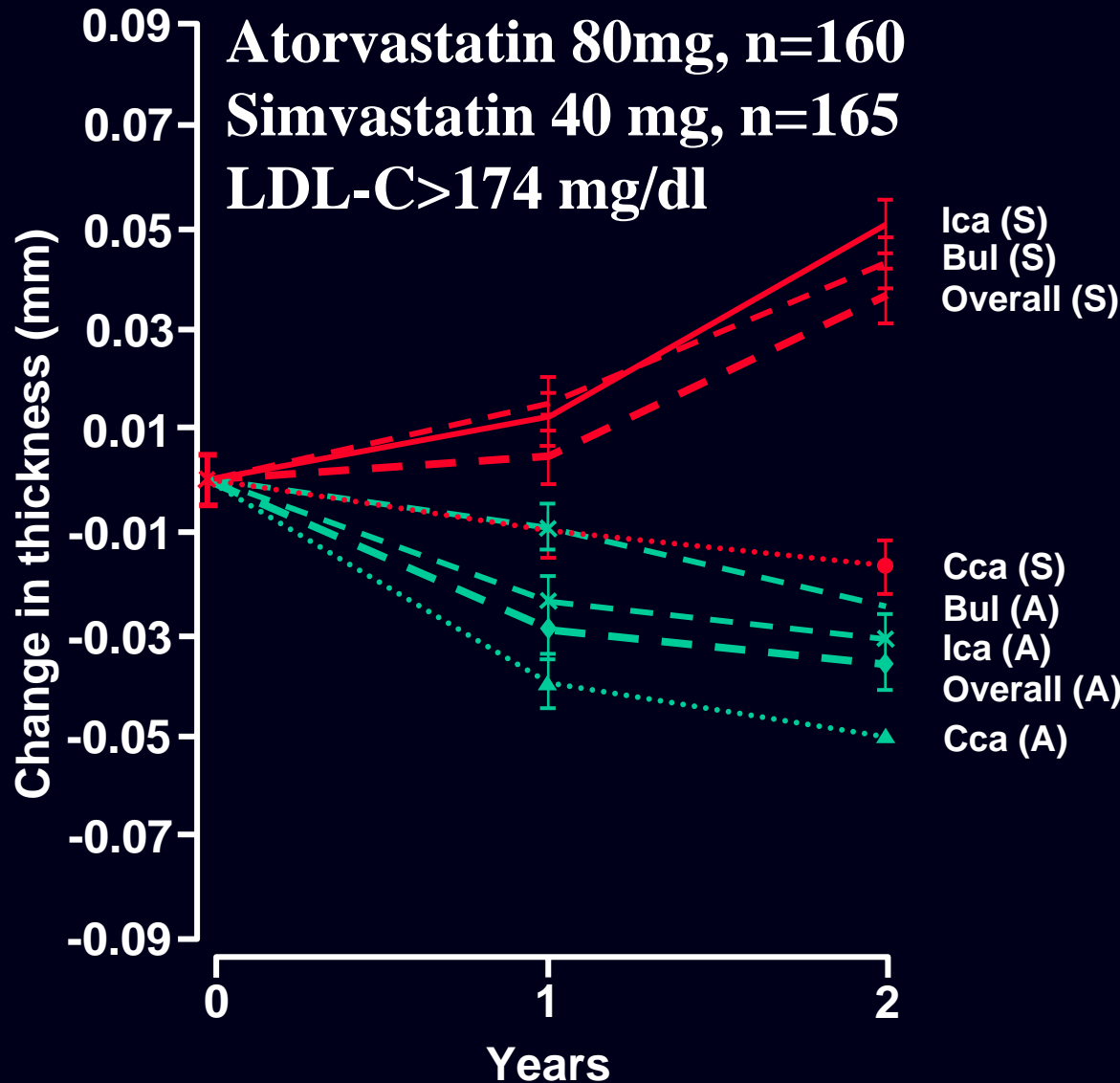
**Lovastatin (20-40 mg/d)  
versus placebo**

**919 asymptomatic  
patients with early  
carotid atherosclerosis**

**Primary outcome:  
3-year change of  
mean maximum IMT**

**In men & women with moderately elevated LDL cholesterol,  
lovastatin reverses progression of IMT in the carotid arteries  
& appears to reduce the risk of major CV events & mortality.**

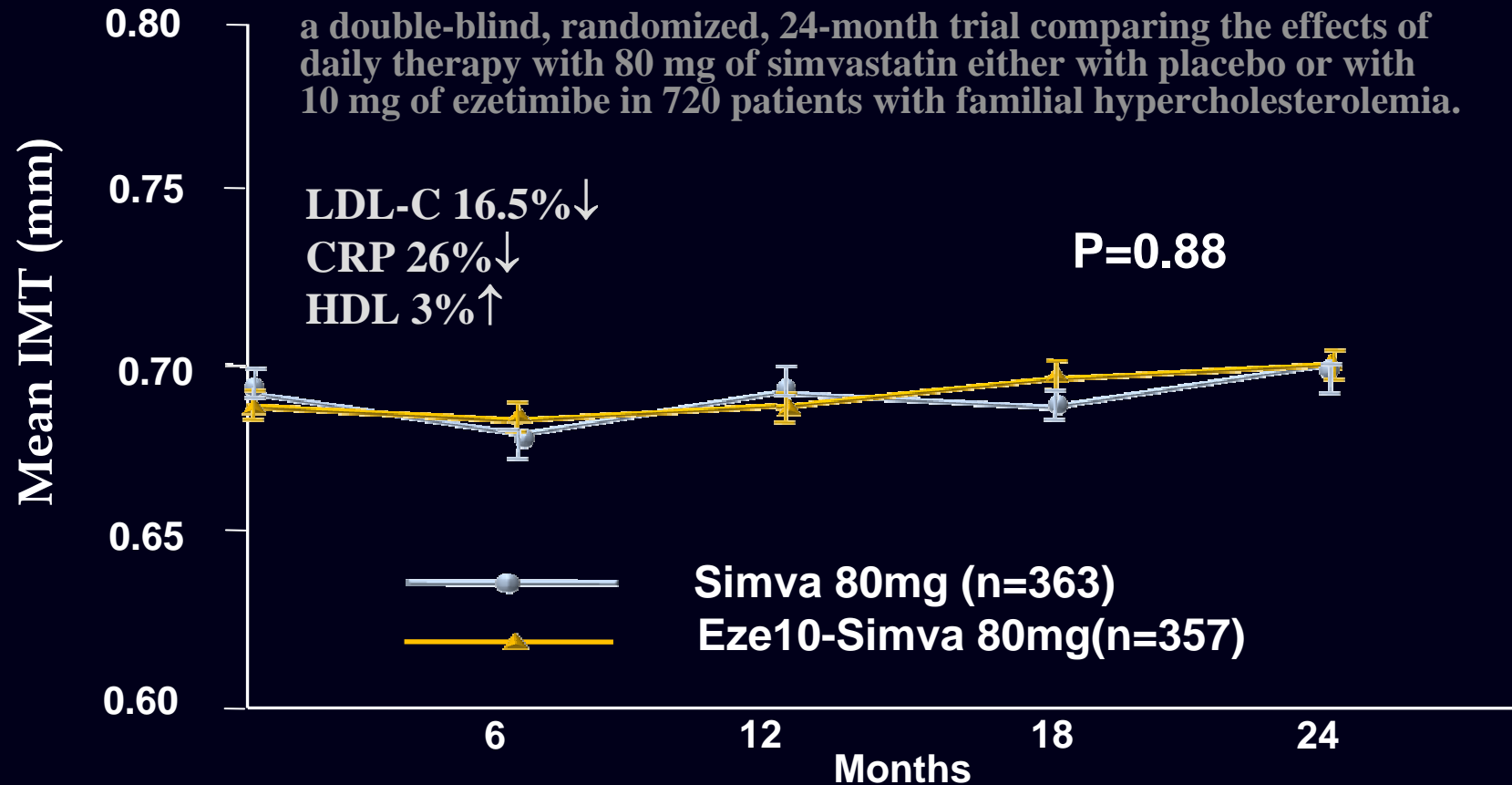
# ASAP



**Aggressive LDL-cholesterol reduction was accompanied by regression of carotid intima media thickness in patients with familial hypercholesterolaemia, whereas conventional LDL lowering was not.**

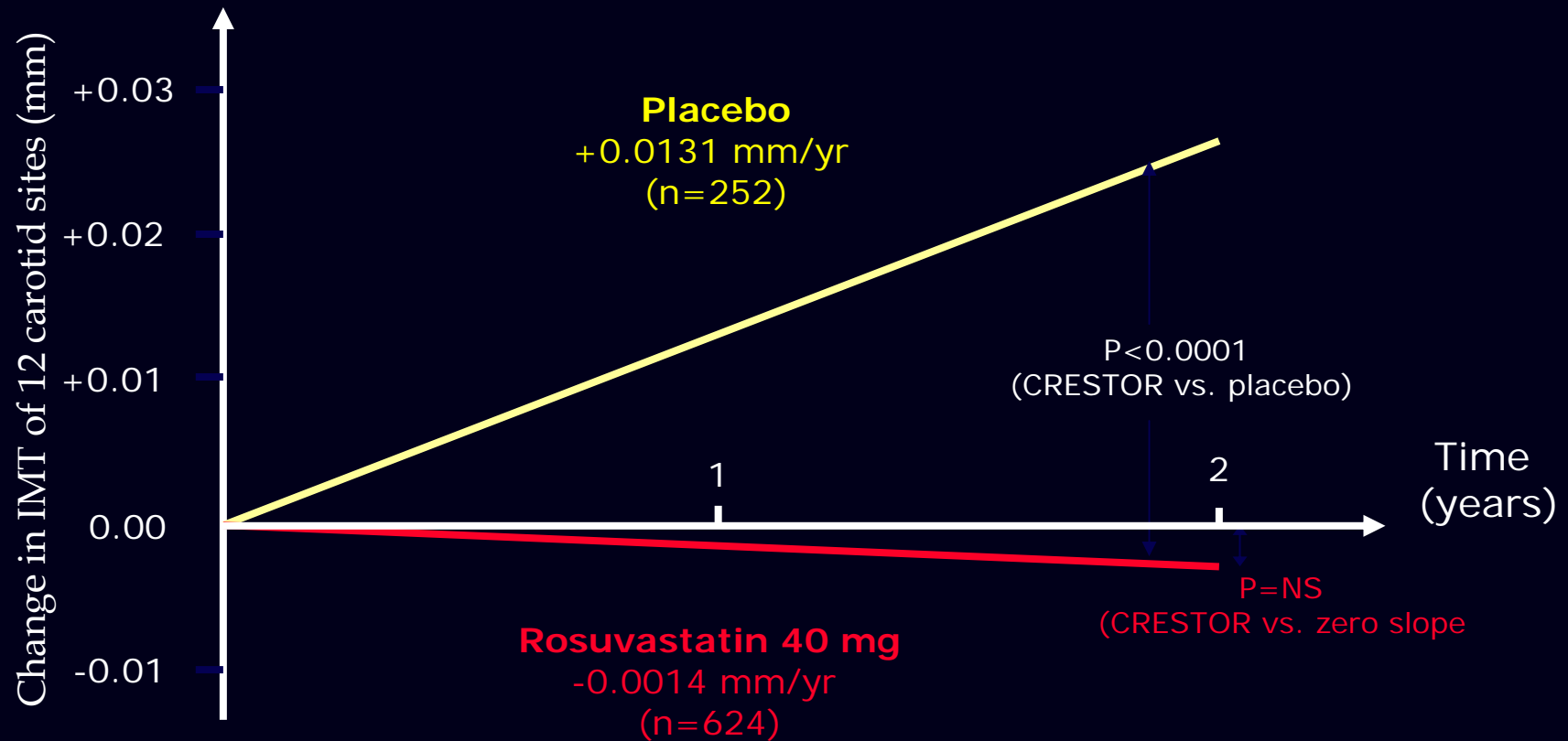
The puzzling result  
different direction

# ENHANCE



In patients with FHC, combined therapy with ezetimibe & simvastatin did not result in a significant difference in changes in IMT, as compared with simvastatin alone.

# METEOR



**In middle-aged adults with an Framingham risk score of less than 10% & evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo.**



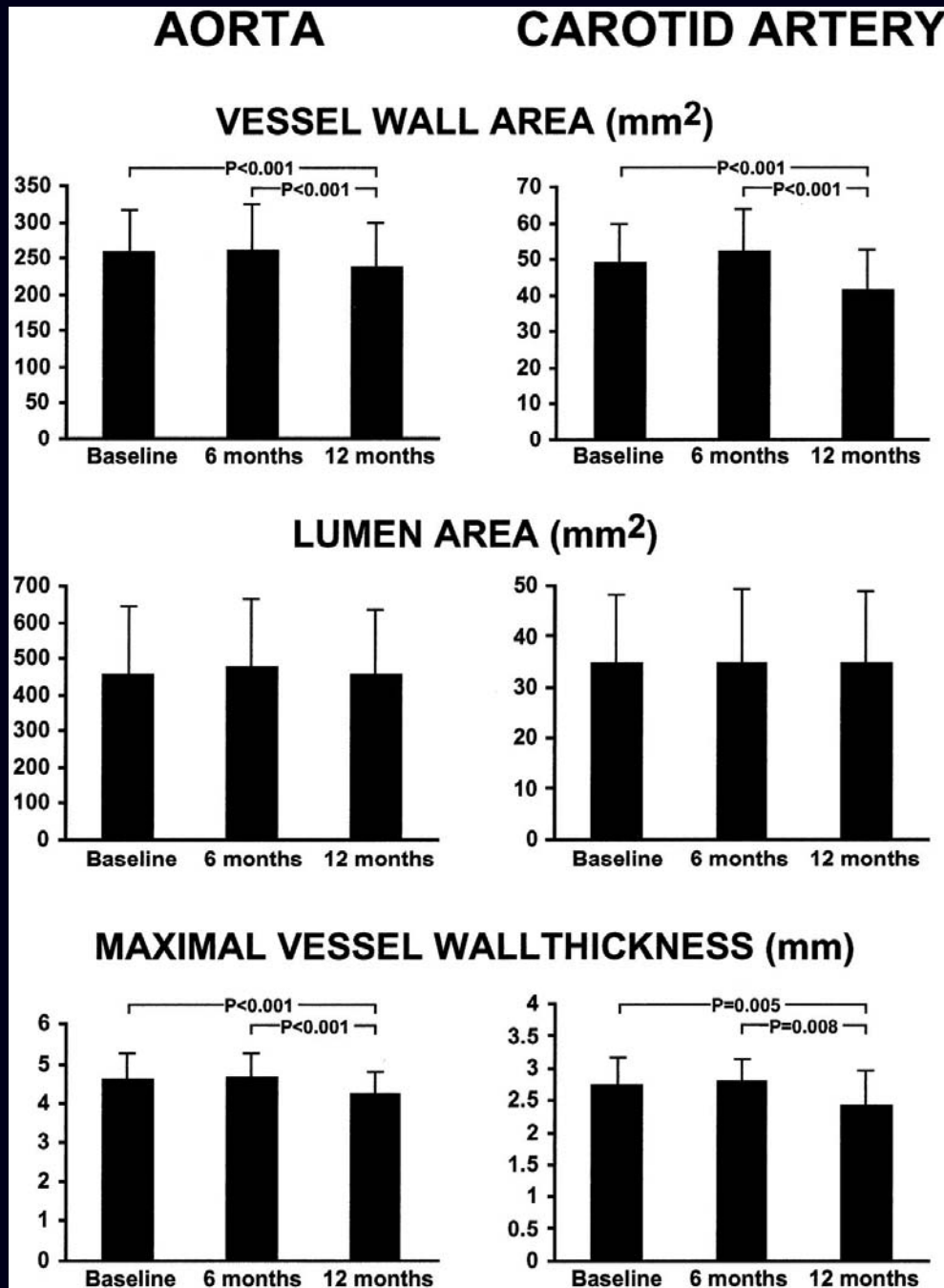
# Summary of Major Lipid-Modifying Trials

<b>Trials</b>	<b>Patients No/ Duration (y)</b>	<b>Treatment</b>	<b>Target</b>	<b>Difference (mm/year)</b>
<b>ACAPS</b>	919/3	L20-40/P1	IMT	-0.015
<b>ARBITER1</b>	161/1	A80/P40	IMT	-0.059
<b>ASAP</b>	325/2	A80/S40	IMT	-0.033
<b>CAIUS</b>	305/3	P40/P1	IMT	-0.0132
<b>ENHANCE</b>		S80+E1/S80	IMT	0.0026
<b>KAPS</b>	424/3	P40/P1	IMT	-0.014
<b>LIPID</b>	522/4	P40/P1	IMT	-0.0155
<b>METEOR</b>	984/2	R40/P1	IMT	-0.0145
<b>ORION</b>	43/2	R80/R5	Volume	No change
<b>PLAC-II</b>	151/3	P20-40/P1	IMT	-0.0082
<b>RADIANCE1</b>	850/2	T60+A/A	IMT	-0.0006
<b>RADIANCE2</b>	752/1.8	T60+A/A	IMT	0.0050

A: atorvastatin, E: ezetrol, L: lovastatin, P: pravastatin, Pl: placebo, R: rosuvastatin, S: simvastatin, T: torcetrapib

# Evidences of Plaque Regression

## Aorta



# Effects of Simvastatin on Atherosclerotic Lesions: MRI Study

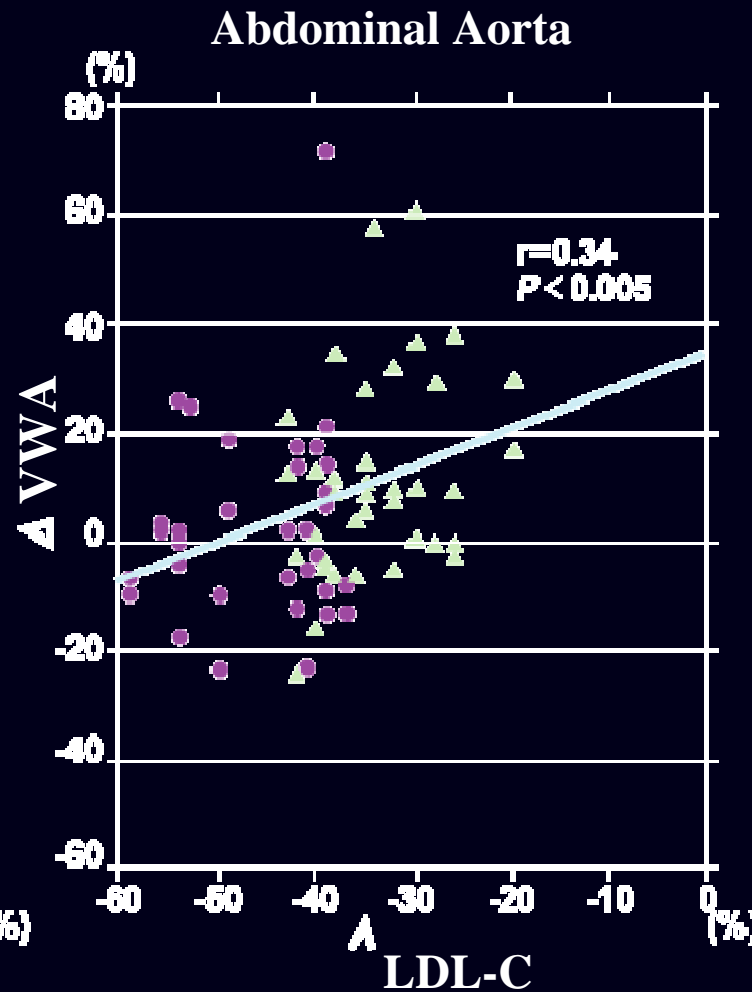
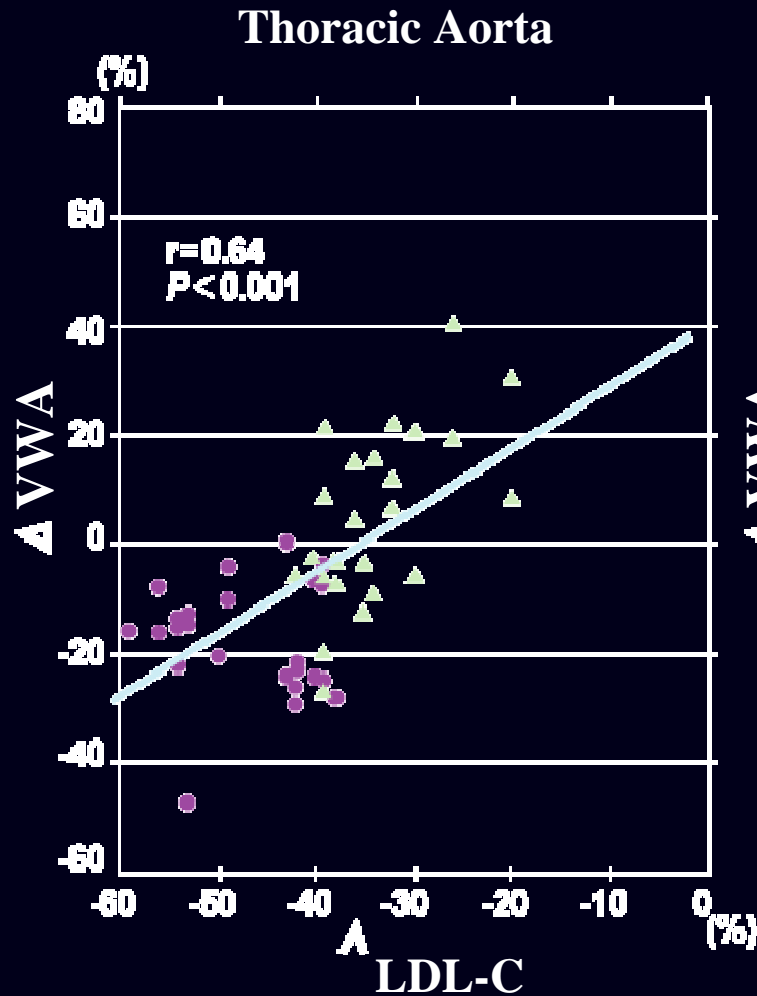
**N=18**

**LDL-C  $\geq$  130 mg/dL,**

**TG  $\leq$  445 mg/dL**

**Effective and maintained lipid-lowering therapy by simvastatin is associated with a significant regression of atherosclerotic lesions (reduction in lipid content -> plaque stabilization).**

# Different Susceptibilities of Thoracic and Abdominal Aortic Plaques to Lipid Lowering

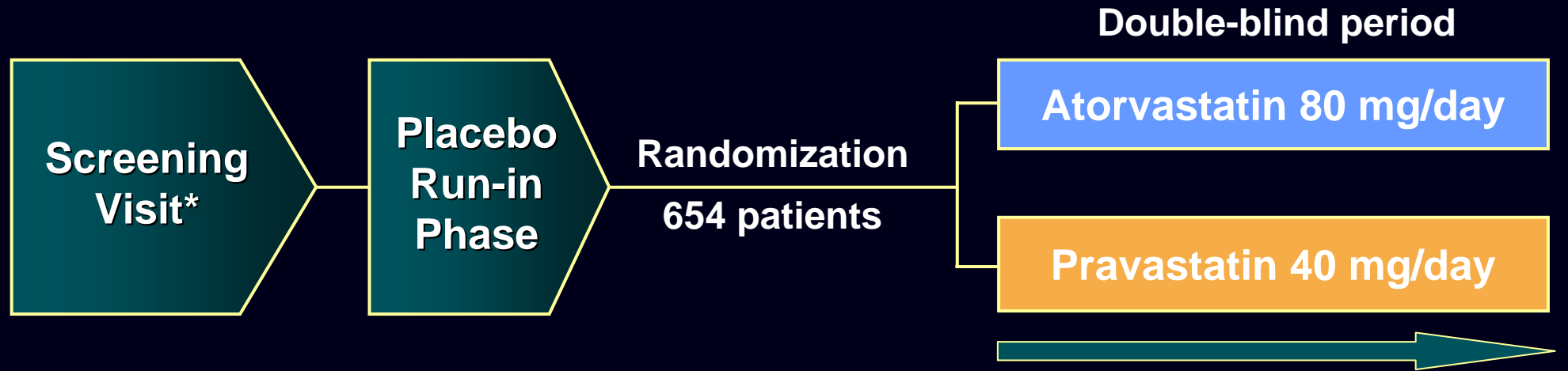


The effects of 20-mg versus 5-mg atorvastatin on thoracic and abdominal aortic plaques in 40 hypercholesterolemic patients (MRI) for 1 year.

Regression of thoracic aortic plaques, whereas only retardation of plaque progression in abdominal aorta.

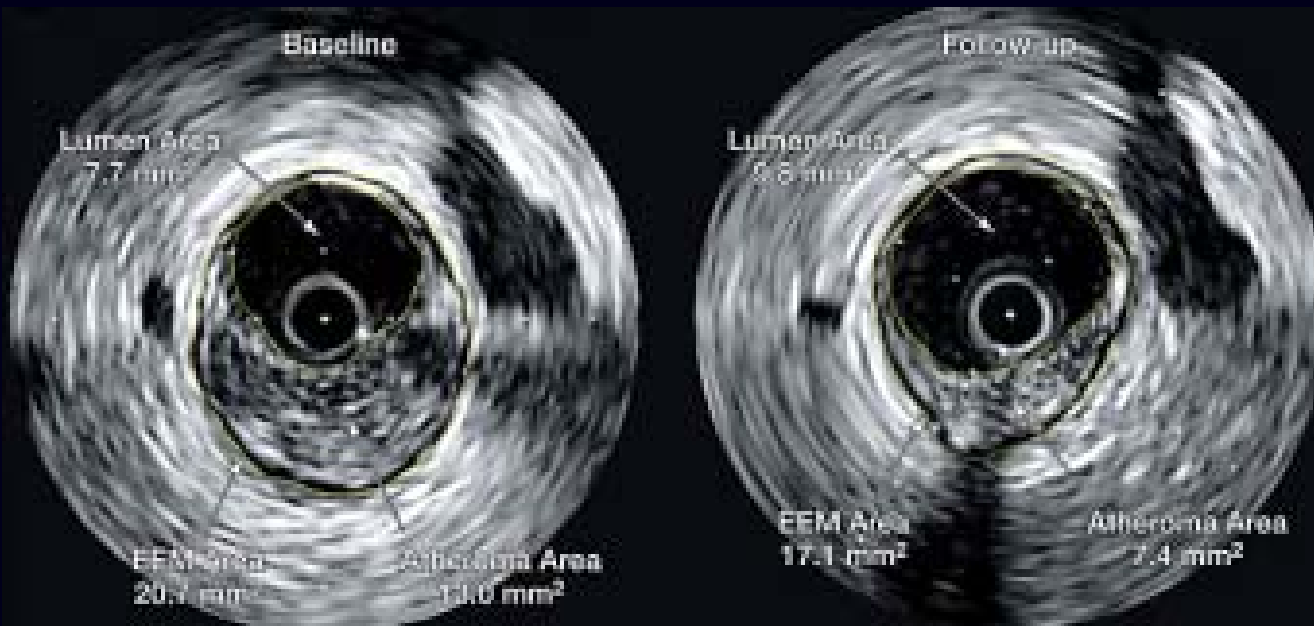
Evidences of  
Plaque Regression  
Coronary Artery

# REVERSAL

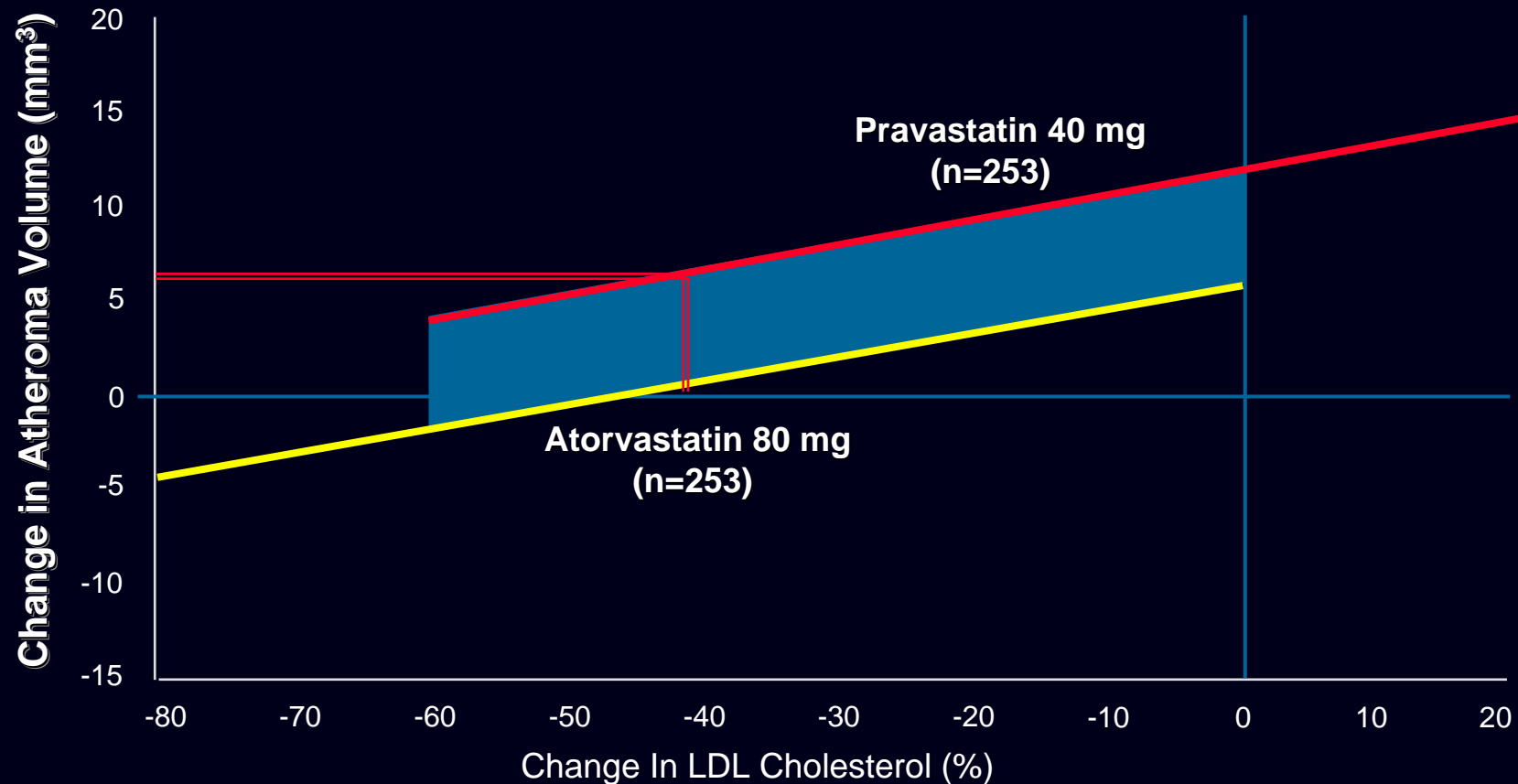


\*Includes baseline intravascular ultrasound (IVUS)

18-month follow-up with IVUS



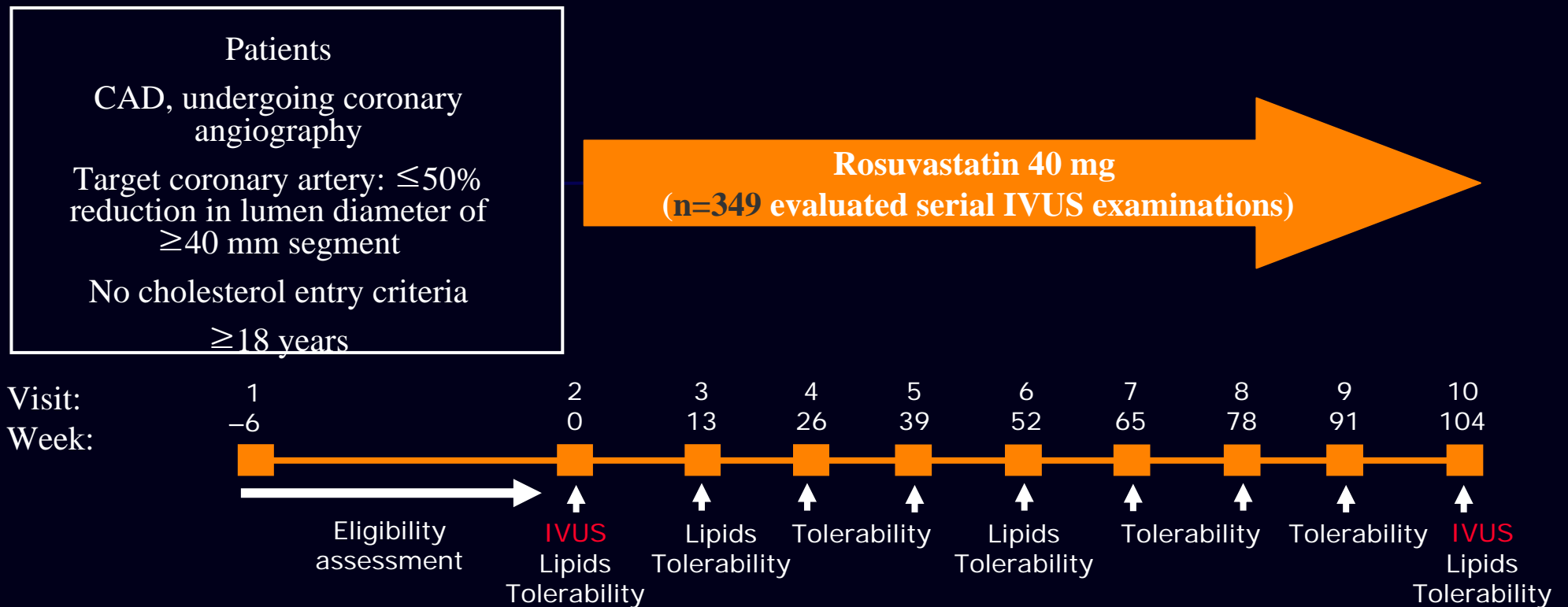
# REVERSAL



**Intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. The progression rate at any level of LDL-C reduction was lower with atorvastatin compared with pravastatin.**

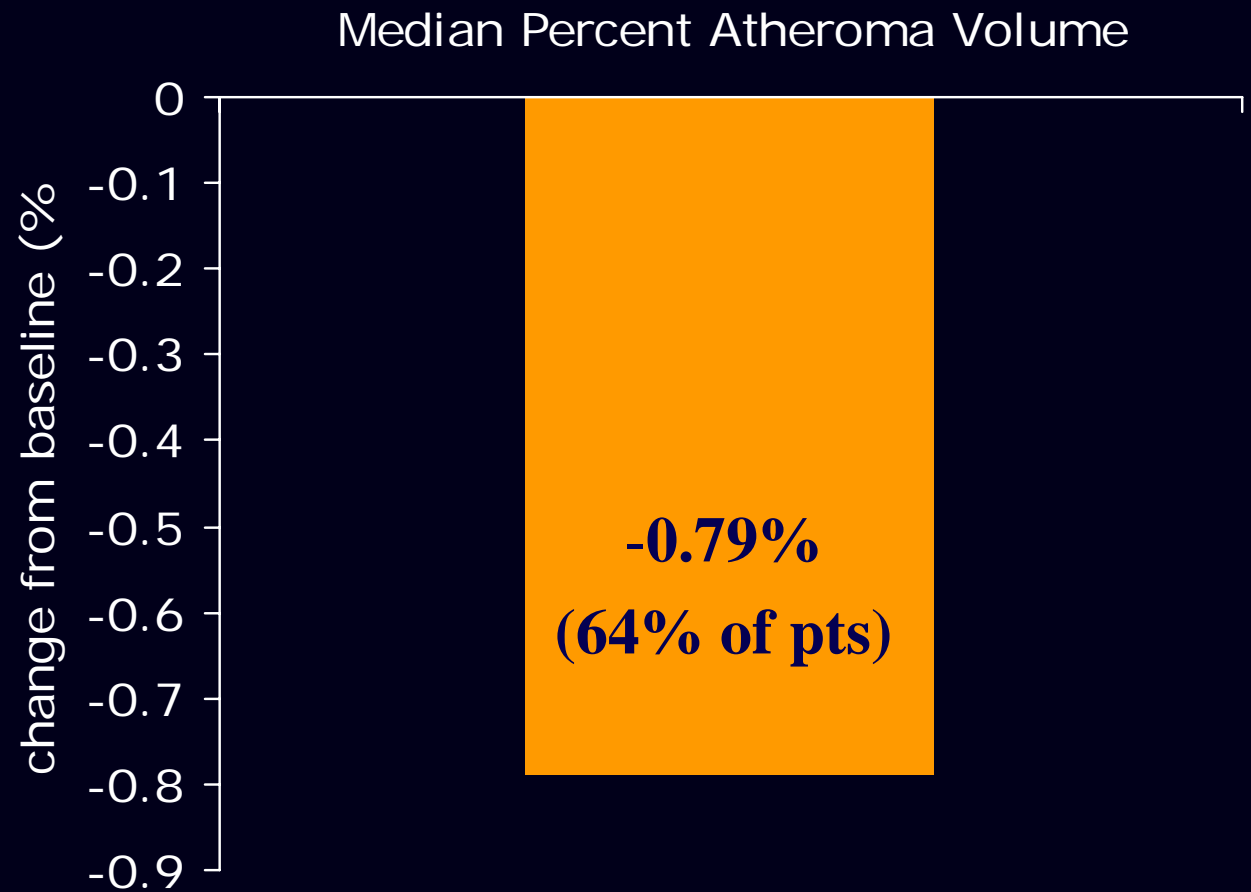
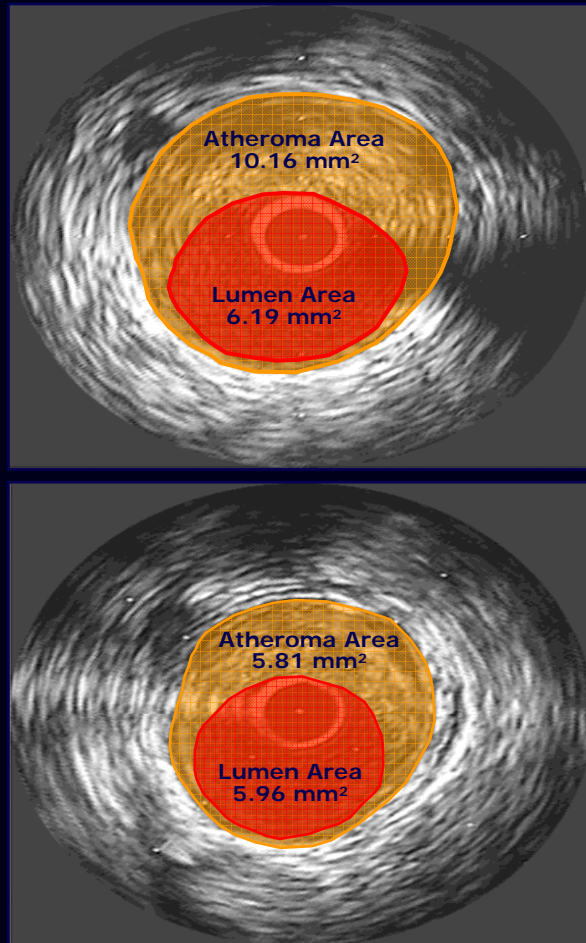
# ASTEROID

To evaluate whether long-term treatment with rosuvastatin 40 mg in CAD pts resulted in coronary plaque regression (single arm study)





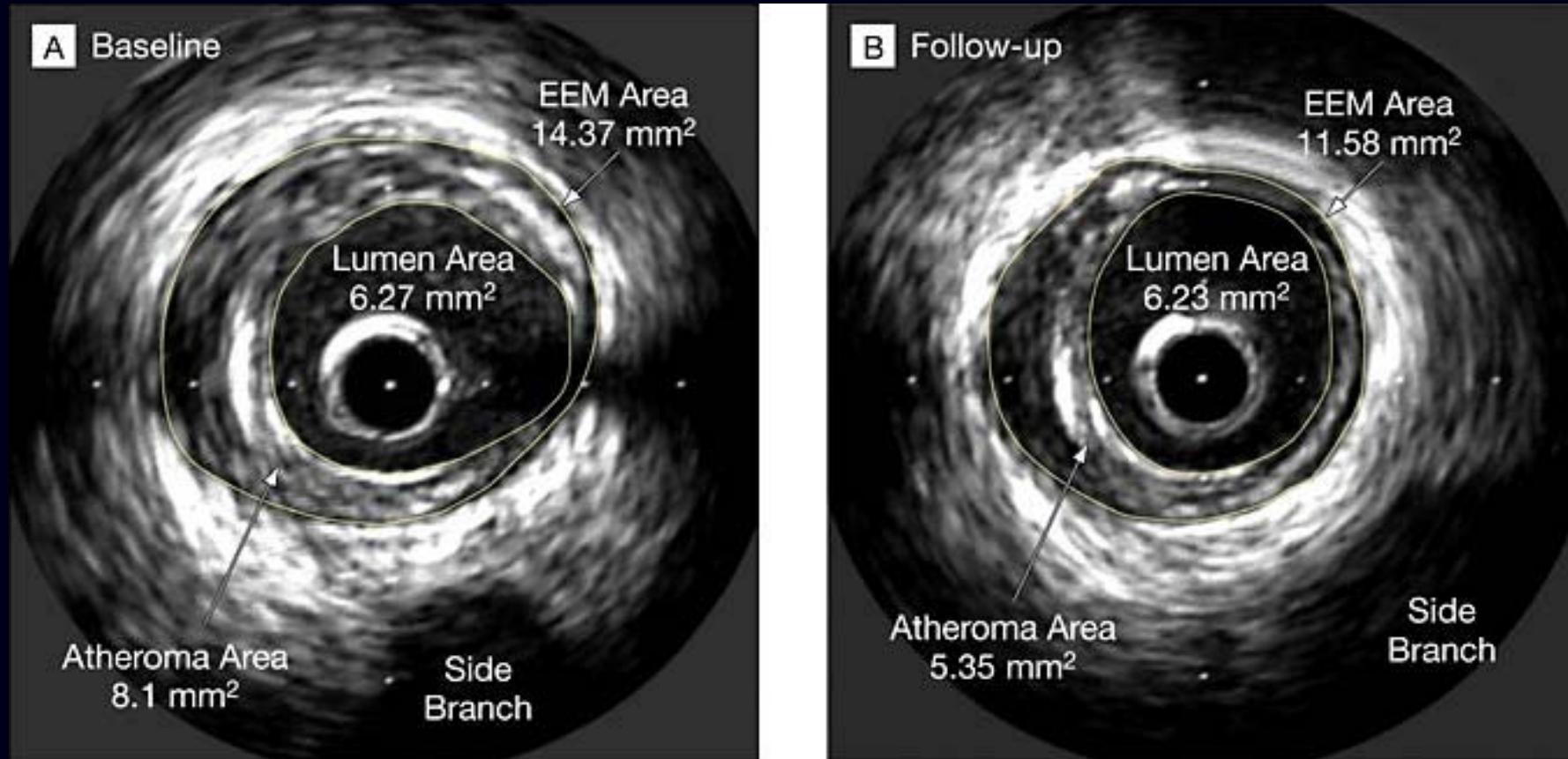
# Primary Endpoint: $\Delta\%$ Atheroma Volume



**Very high-intensity statin therapy using rosuvastatin 40mg/d resulted in significant regression of atherosclerosis,**

Much heat, little light

## Effect of Recombinant ApoA-I Milano (HDL Mimetics) on Coronary Atherosclerosis in Pts With ACS



*-14.1 mm<sup>3</sup> or a 4.2% decrease from baseline*

**A recombinant ApoA-I Milano/phospholipid complex (ETC-216) administered intravenously for 5 doses at weekly intervals produced significant regression of coronary atherosclerosis as measured by IVUS.**

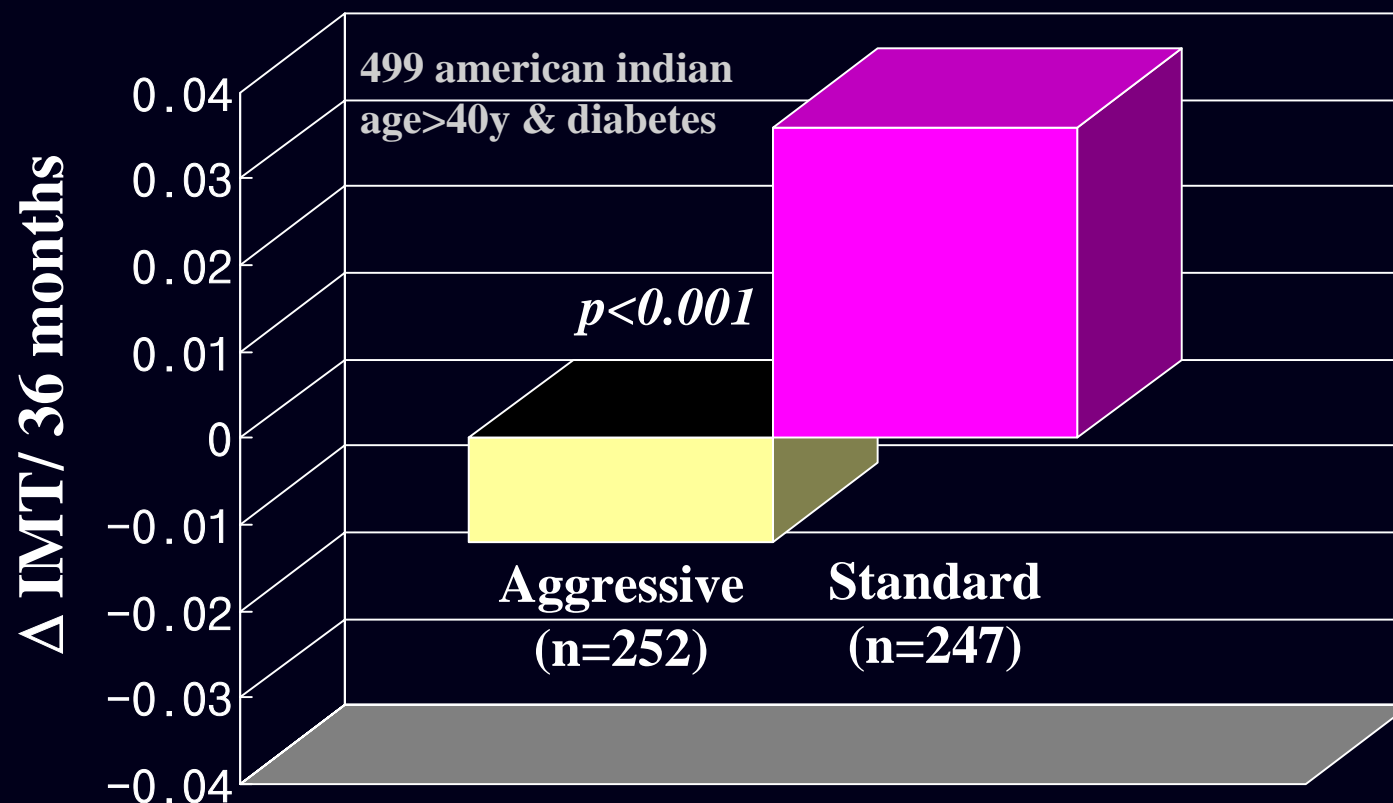
# Summary

There are convincing evidences to support that high-dose statin or HDL-raising therapies may induce regression of mild to moderate atherosclerotic lesions in humans.

# Presentation

- Evidences of plaque regression
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## Effect of Lower Targets for BP & LDL Cholesterol on Atherosclerosis in DM The SANDS Randomized Trial



The probability of a decrease in IMT was significantly related to decrease in LDL-C but not significantly related to a decrease in SBP.

Conversely, probability of decreases in LVMI were significantly related to decreases in SBP but not to LDL-C decreases.

Reducing LDL-C (<70mg/dl vs. 100) & SBP (<115mmHg vs. 130) to lower targets resulted in regression of carotid IMT & greater decrease in LV mass in type 2 DM.

# REVERSAL: Continuous Relationship between LDL-C, CRP, and Percent Atheroma Volume

Change In Percent  
Atheroma Volume (%)

Change In Percent  
Atheroma Volume (%)

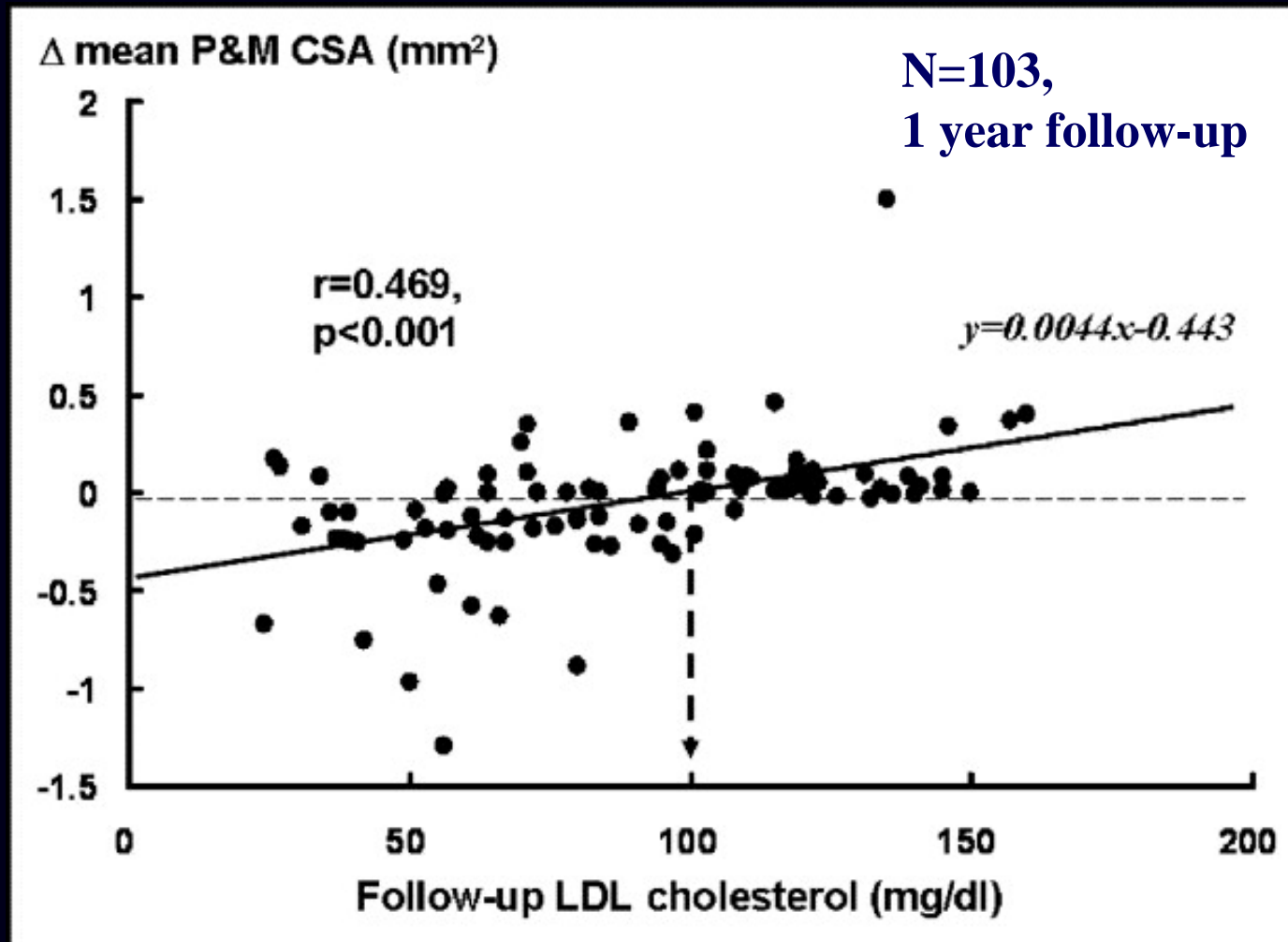
**In REVERSAL,**

Greatest decrease in disease progression observed among patients with greatest reductions in CRP for any given change in LDL-C

Change In LDL-C (mg/dL)

Change In CRP (mg/L)

# Usefulness of Follow-Up LDL-C Level as an Independent Predictor of Changes of Coronary Atherosclerotic Plaque Size After *Statin* Therapy



When patients achieved a follow-up LDL cholesterol level <100 mg/dl, regression or no progression of coronary plaque was expected.

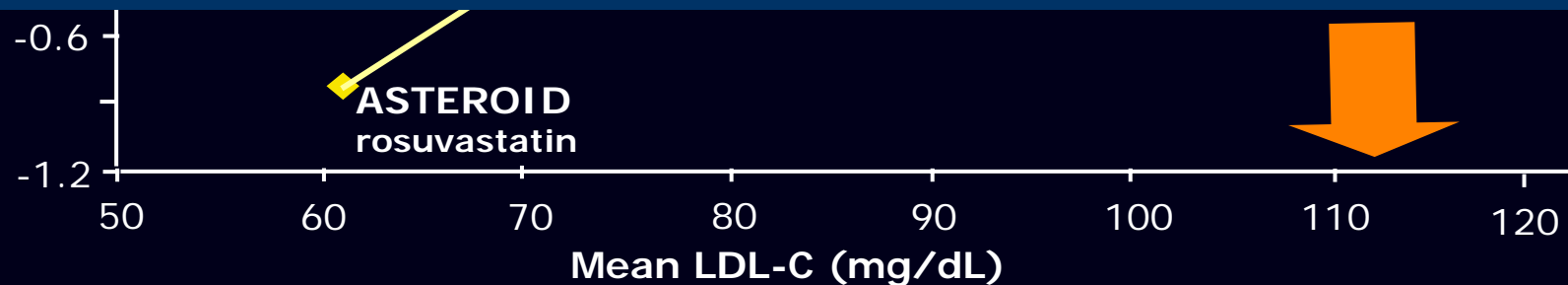
# Relationship between LDL-C levels & change in % atheroma volume for several IVUS trials

1.8  
 $R^2 = 0.97$

REVERSAL  
rosuvastatin

## In ASTEROID,

There was no plaque regression in patients with LDL-C > 100 mg/dl,  
and little change in patients with LDL-C of 70-100 mg/dl.  
Plaque regression was only seen in patients with LDL-C ≤ 70 mg/dl.





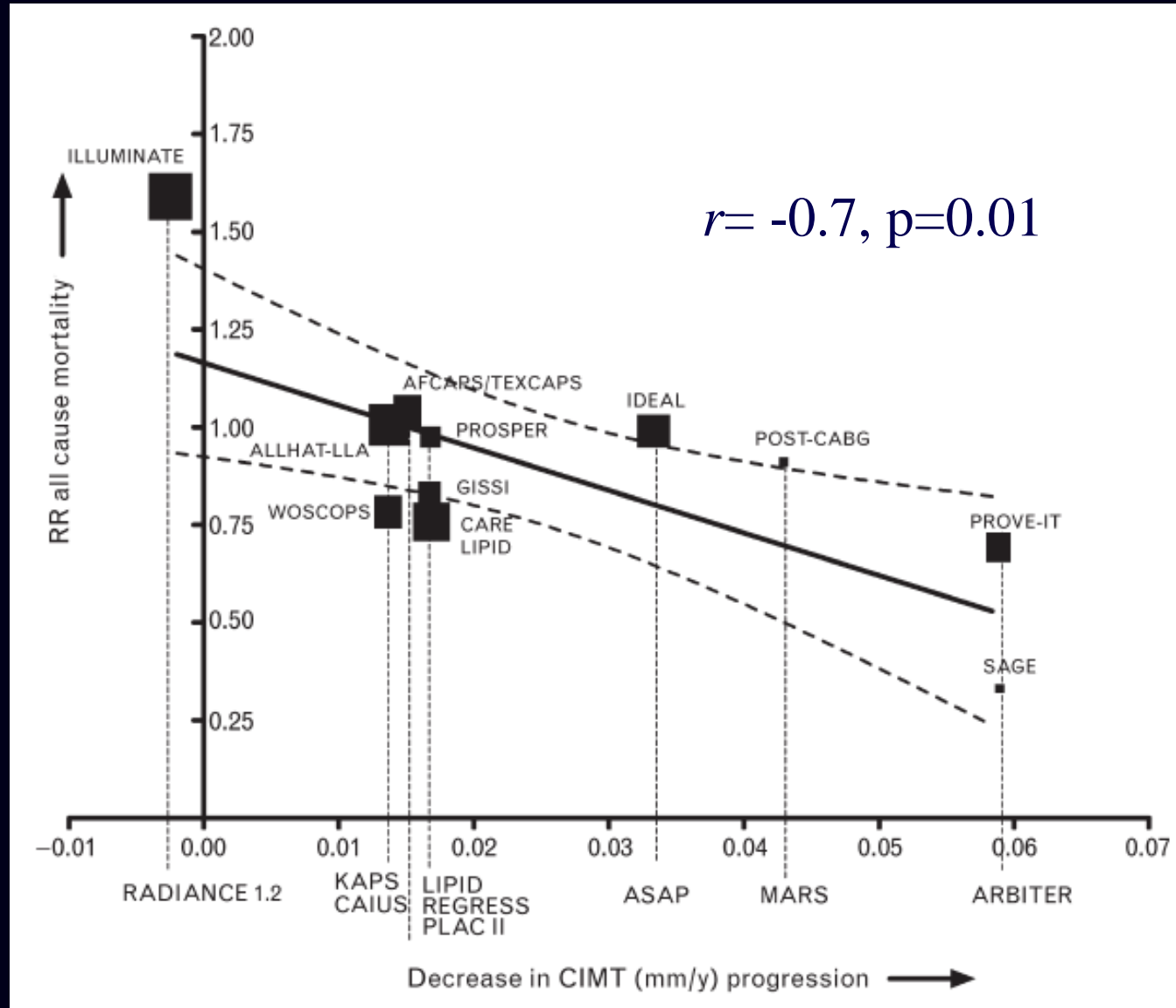
# Summary

- Plaque regression is associated with a substantial reduction of LDL-C, and lipids and inflammatory substances may be responsible for this change.
- It remains uncertain whether plaque consisting of connective tissue and calcium may be regressive.

# Presentation

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# Association between Carotid IMT and Clinical Endpoints



**Are surrogate imaging markers of the arterial wall are representative for clinical outcomes ?**

**Imaging trials and clinical endpoints trials that evaluated similar drugs indicates good correlations between CIMT & clinical events.**

## **Limitations:**

- different imaging protocols
- different outcomes measures

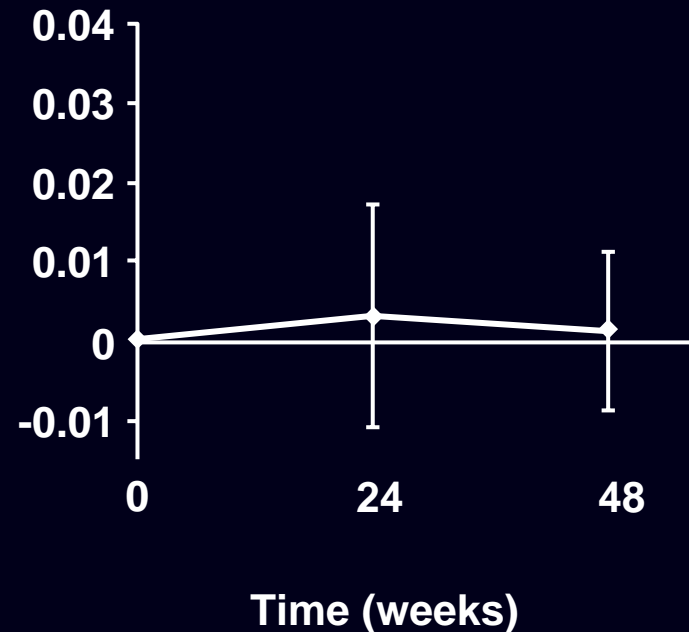
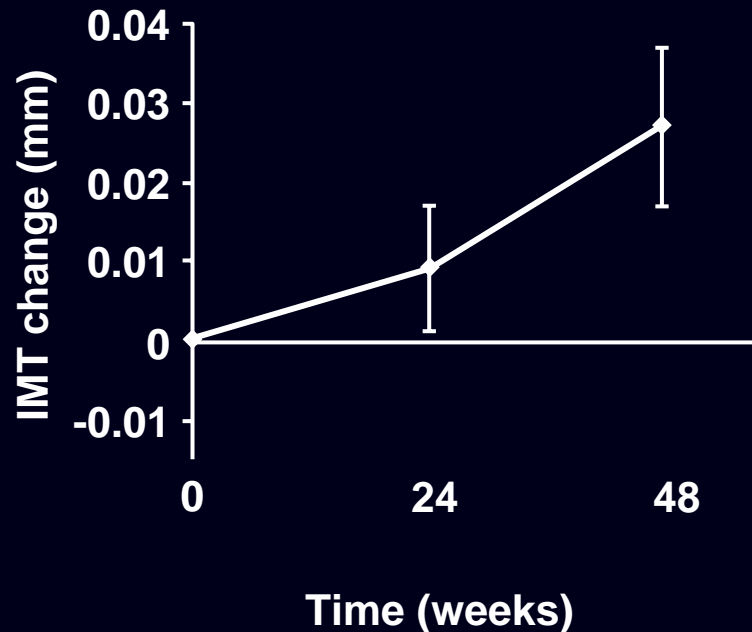
# Effect of Rosiglitazone on Carotid IMT Progression in CAD Patients Without DM

Placebo

Rosiglitazone 8 mg/day

Progression rate = 0.031 mm/48 weeks  
(0.0016, 0.0604)

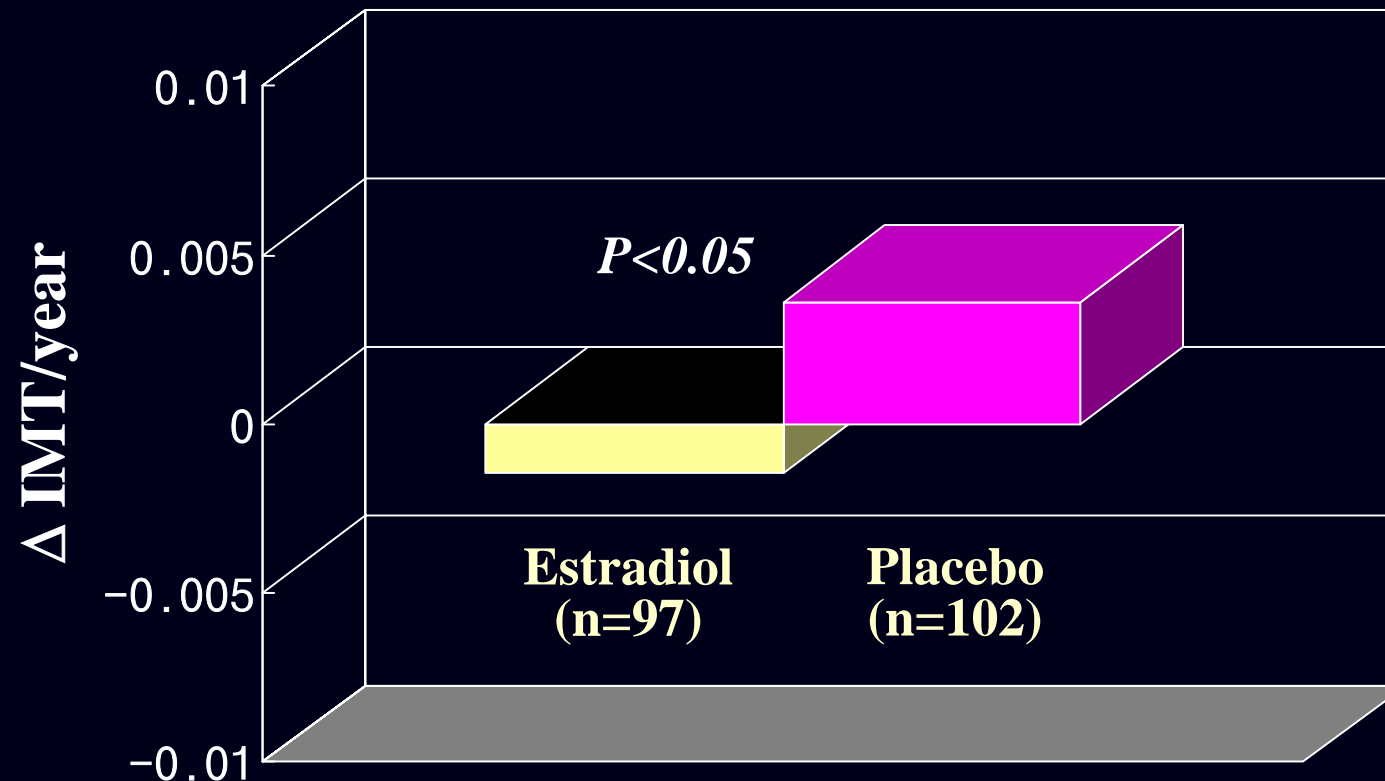
Progression rate = -0.012 mm/48 week  
(-0.0414, 0.0174)



**Rosiglitazone reduces common carotid IMT progression in nondiabetic CAD patients, & insulin-sensitization may be one contributory mechanism.**

An effective surrogate?

## Estrogen in the Prevention of Atherosclerosis A Randomized, Double-Blind, Placebo-Controlled Trial

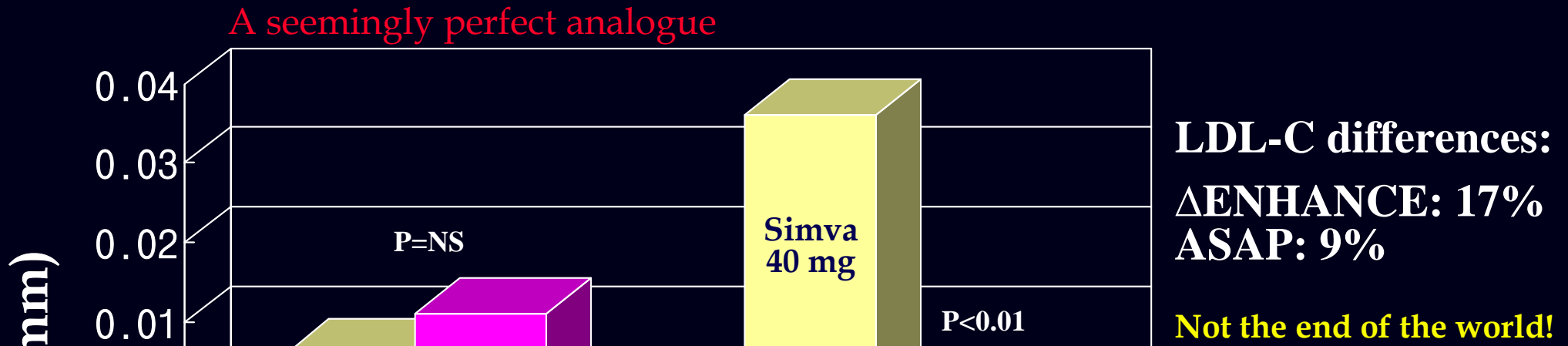


The average rate of progression of IMT was slower in healthy postmenopausal women taking unopposed ERT with  $17\beta$ -estradiol than in women taking placebo

*A very different interpretation*

# ENHANCE vs. ASAP

## What's the differences?



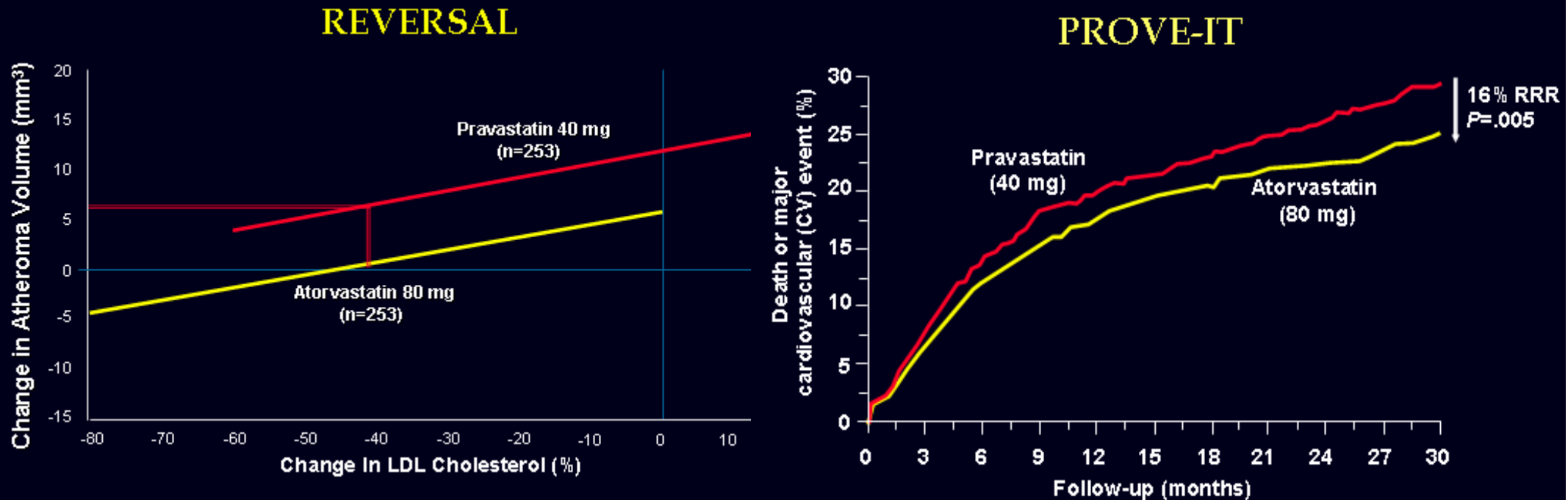
The results of **IMPROVE-IT**, which will not be available until 2012, are expected not only to help define the role of ezetimibe in the treatment of hypercholesterolemia but also to provide insight into the use of IMT as a surrogate indicator of coronary events.

-0.04

**ENHANCE**

**ASAP**

# Association between Coronary Plaque Progression as Measured by IVUS & CV Events



The REVERSAL study used the same treatment regimen as the PROVE-IT. Although the REVERSAL & PROVE-IT studies were distinct studies, their results provided evidence that plaque progression measured by IVUS is predictive of an increased risk of CV events.

The same direction  
**Stunning reversals**

## Torcetrapib & Regression ILLUSTRATE

Placebo

torcetrapib

### IVUS-derived indexes of coronary plaque progression

Pitfall of PAV (average atheroma area/average EEM area)

- 5%↑ of atheroma (progression), 10%↑ of EEM (positive remodeling)  
→ 4.5%↓ of PAV (regression)

It remains uncertain what's the best surrogate for clinical benefits.

Total  
└ -10





# Summary

- **The CIMT or IVUS studies provide proof of concept, giving us the answer with only a few hundred patients**
- **Although plaque regression does not guarantee a reduction in the rate of clinical events, it may not be expected without a reduction in plaque progression.**
- **However, imaging surrogates will not be a substitute for clinical endpoint trials because regression does not necessary mean plaque stabilization.**

# Presentation

- Evidences of plaque regression
- Predictors of plaque regression
- Clinical significance of regression
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# Effect of Rosuvastatin Therapy on Coronary Artery Stenosis Assessed by QCA in ASTEROID

## Clinically Relevant Changes

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Stenosis reduced by	$\geq 10\%$ (regression*)	22	7.5%
Stenosis changed by	$< 10\%$	261	89.4%
Stenosis increased by	$\geq 10\%$ (progression*)	9	3.1%

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\* Proportion of regressors greater than progressors, both  $p < 0.03$

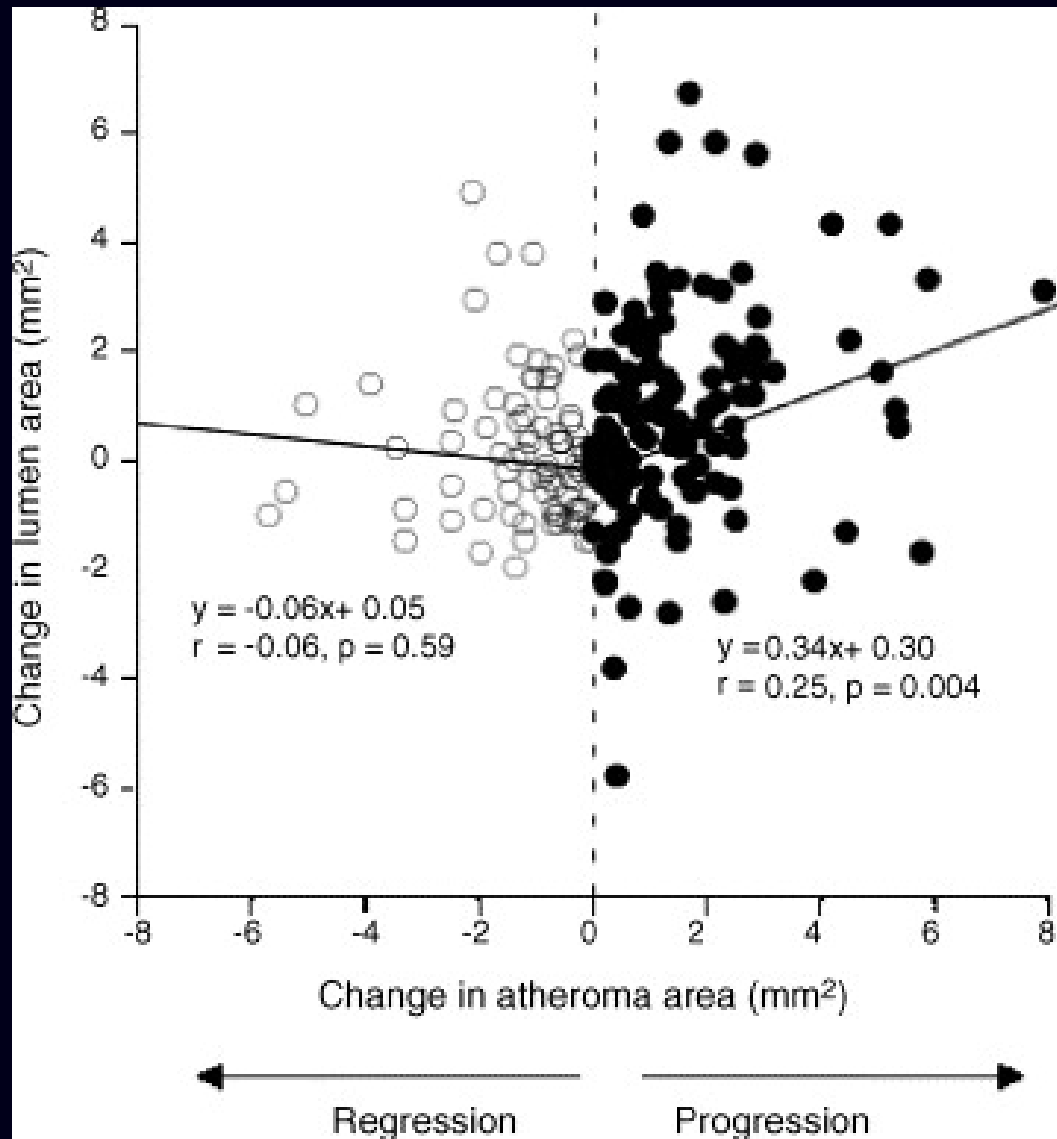
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MLD larger by	$\geq 0.2\text{mm}$ (regression*)	34	12.1%
MLD Change	$< 0.2\text{mm}$	261	89.4%
MLD smaller by	$\geq 0.2\text{mm}$ (progression*)	9	3.1%

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\* Proportion of regressors greater than progressors, both  $p < 0.03$

## Paradoxical lumen loss



Minimal Regression  
Is Exchanged  
for Lumen Loss.

Progression of coronary atherosclerosis can be associated with a paradoxical increase in lumen cross-sectional area, whereas regression is not associated with any change in lumen area (REVERSAL trial).

More than just regression!

## Future Perspective and Unanswered Questions

- Study duration:
  - Most studies lasted for only  $\leq 2$  years

### Plaque Quantity vs. Quality

- Minimal cosmetic improvement does not improve myocardial ischemia.
- Plaque regression does not necessary mean plaque stabilization, requiring imaging tools for accurate evaluation of plaque quality.

Plaque regression,  
a good but not great surrogate

# Conclusions

Regression is **a surrogate marker (unproven stand-in)** waiting for definitive outcome trials.

Any drug taken by patients every day for the rest of their life should be backed with **accepted outcome data (Level A evidence)**.