Atherosclerosis Regression

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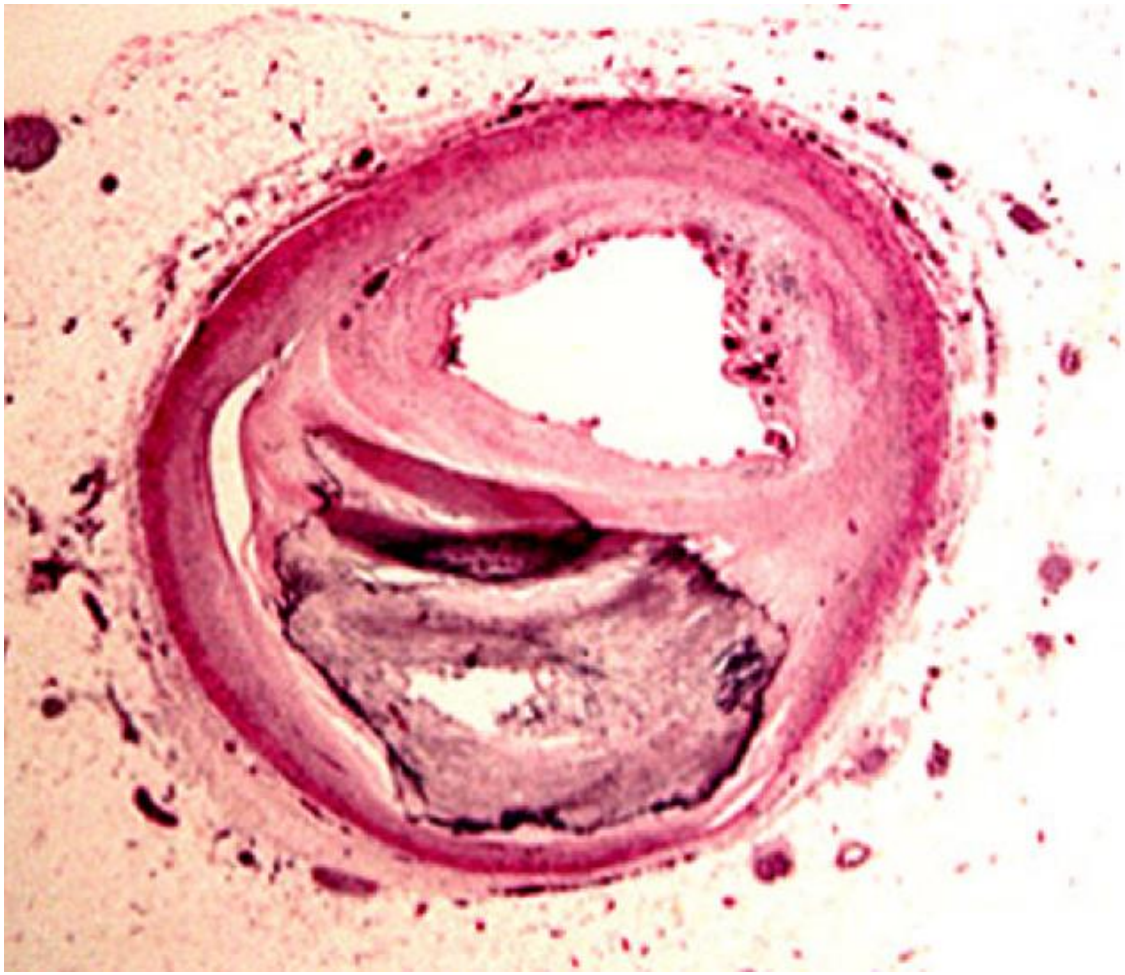
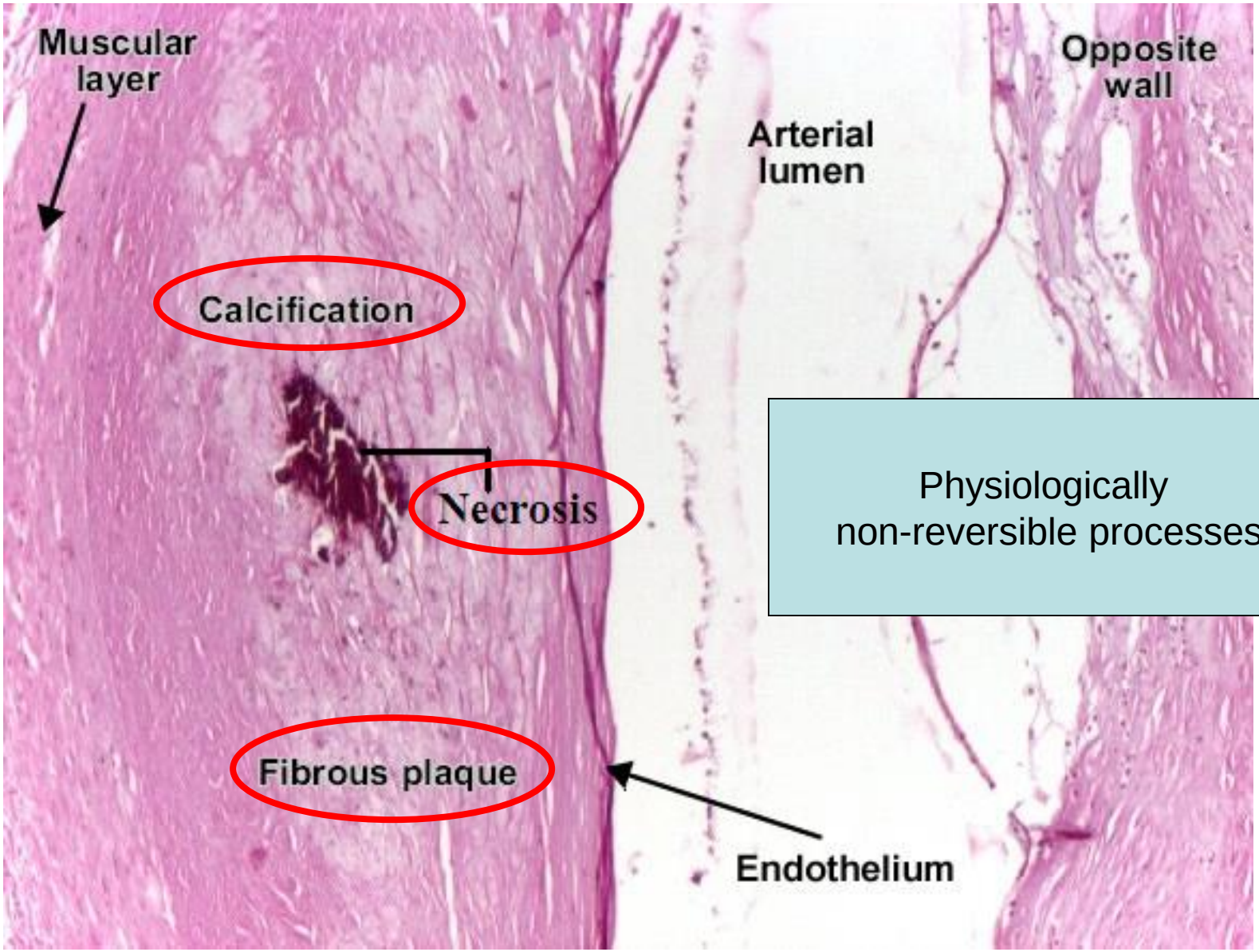
Over the decades it was difficult to assume that human atheromata can regress…



…because



Physiologically non-reversible processes

Numerous other processes involved in atherogenesis

-oxidation,

-injury,

-cellular transformations resembling carcinogenesis

are all permanent changes

Numerous animal studies since 1920…

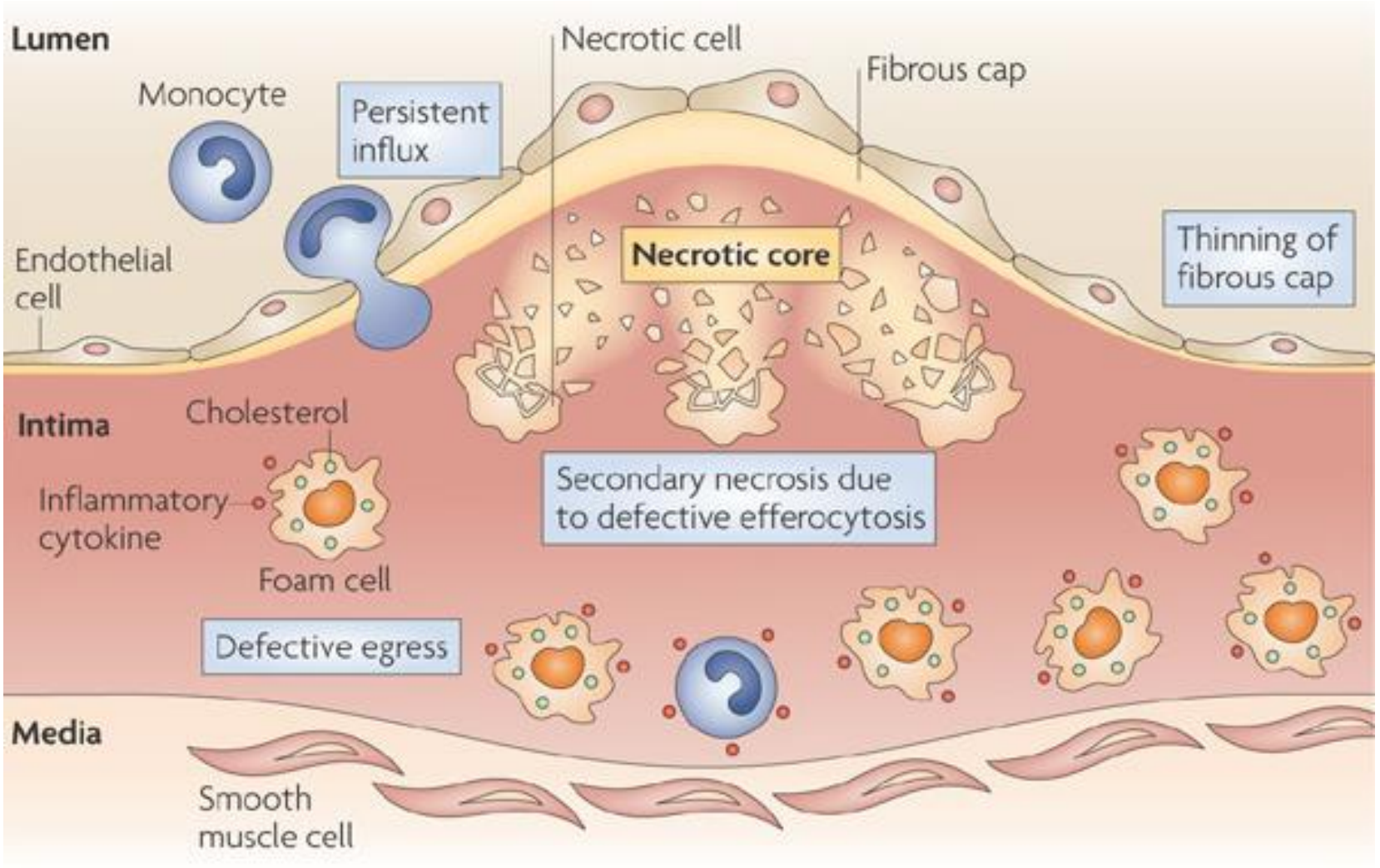
- Anichkov and colleagues- reported that low-fat diet over 2–3 years as well as intravenous bolus injections of phosphatidylcholine (PC) demonstrating substantial shrinkage of atherosclerotic lesions in rabbits
- Maruffo and Portman; Wissler and Vesselinovich- advanced arterial lesions underwent shrinkage with a low-fat or linoleate rich diets in squirrel monkeys

Intrerventions that proved effective

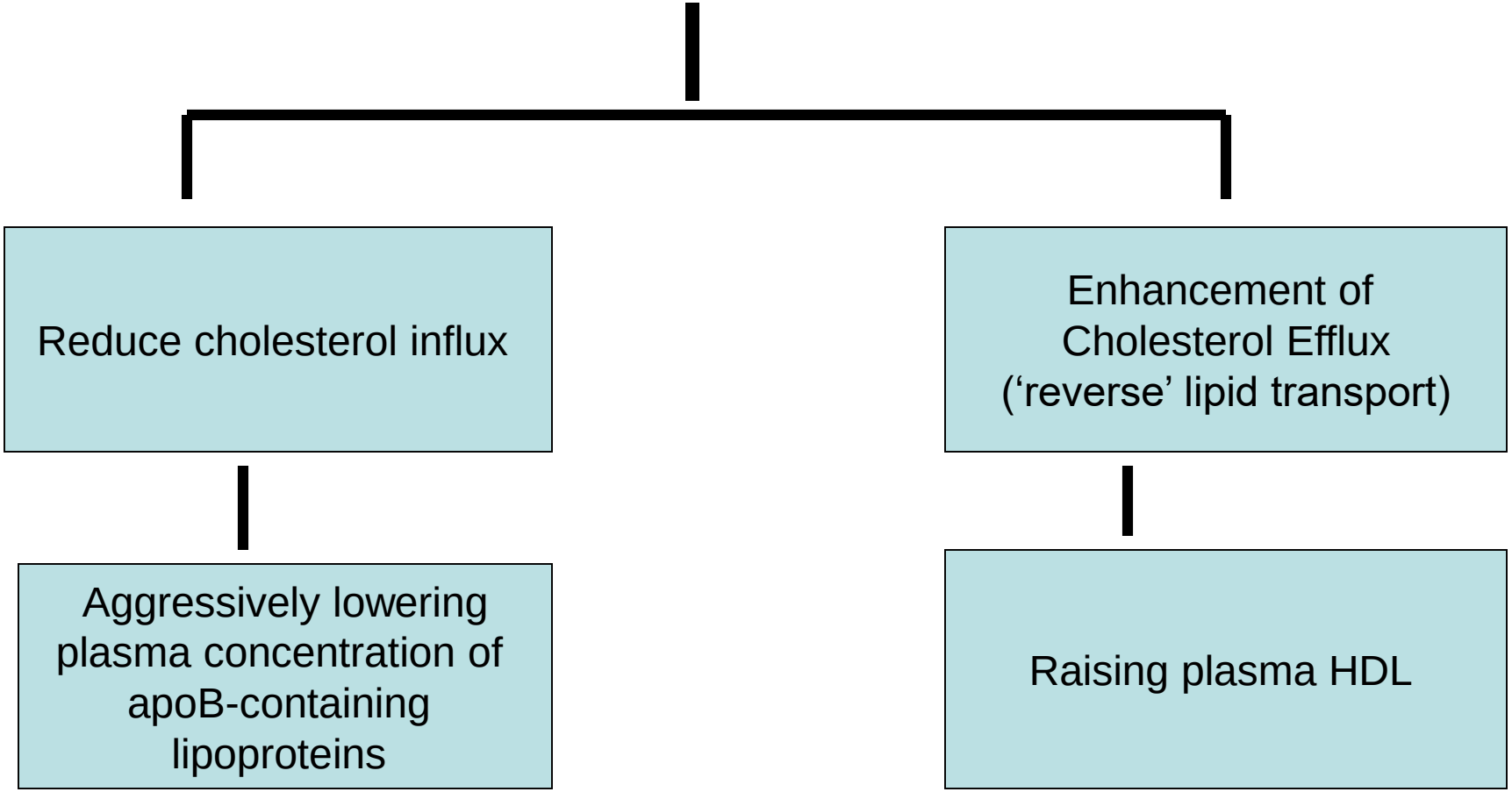
- Shrinkage of atheromata in rabbits via injections of HDL or HDL-like apolipoprotein A-I (apoA-I) and PC disks.
- Gene transfer to achieve plaque regression in mice adenoviral vector containing a human apoA-I cDNA.
- Rapidly remodelling of plaques in mice by infusion of recombinant apoA-IMilano/PC complexes.
- Gene transfer strategy causing hepatic overexpression of apoE, which increases the clearance of plasma atherogenic lipoproteins through receptors in the liver for LDL.

When cholesterol influx exceeds cholesterol efflux there is atherosclerosis

Biology of atheromatous plaques



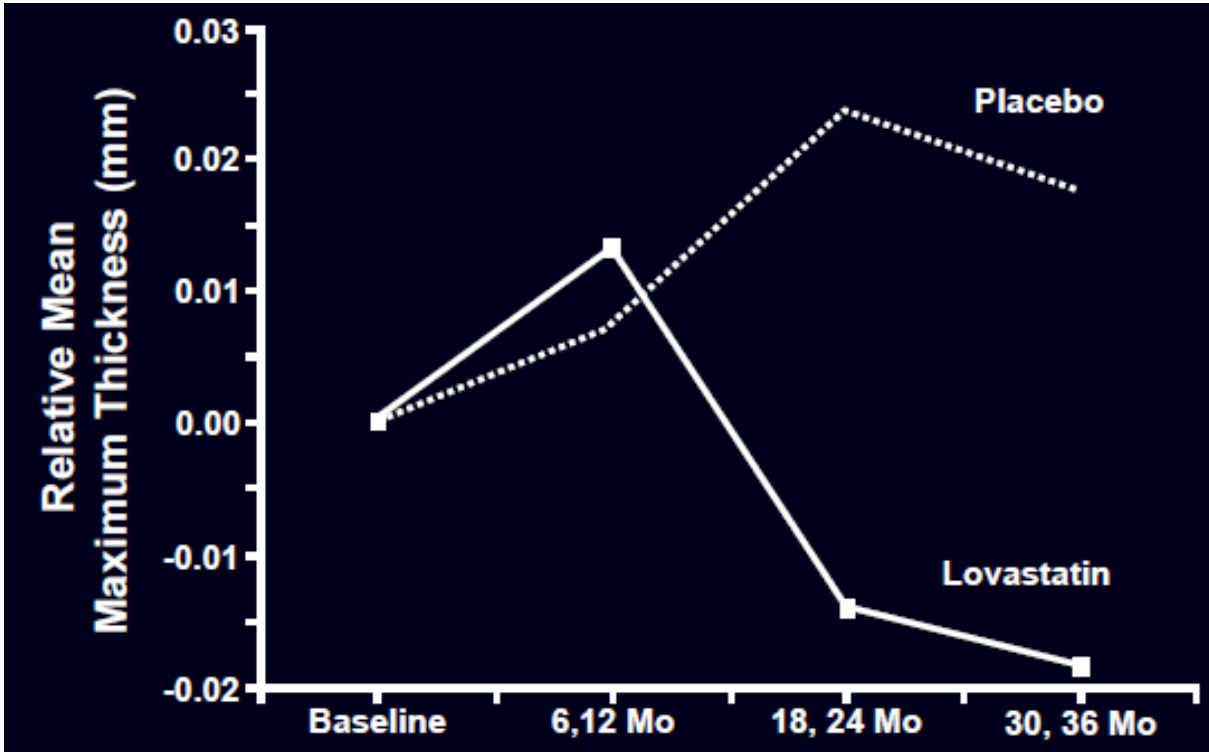
Successful regression of atherosclerosis



Evidences of Plaque Regression

Carotid Artery

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



Lovastatin (20-40 mg/d) versus placebo

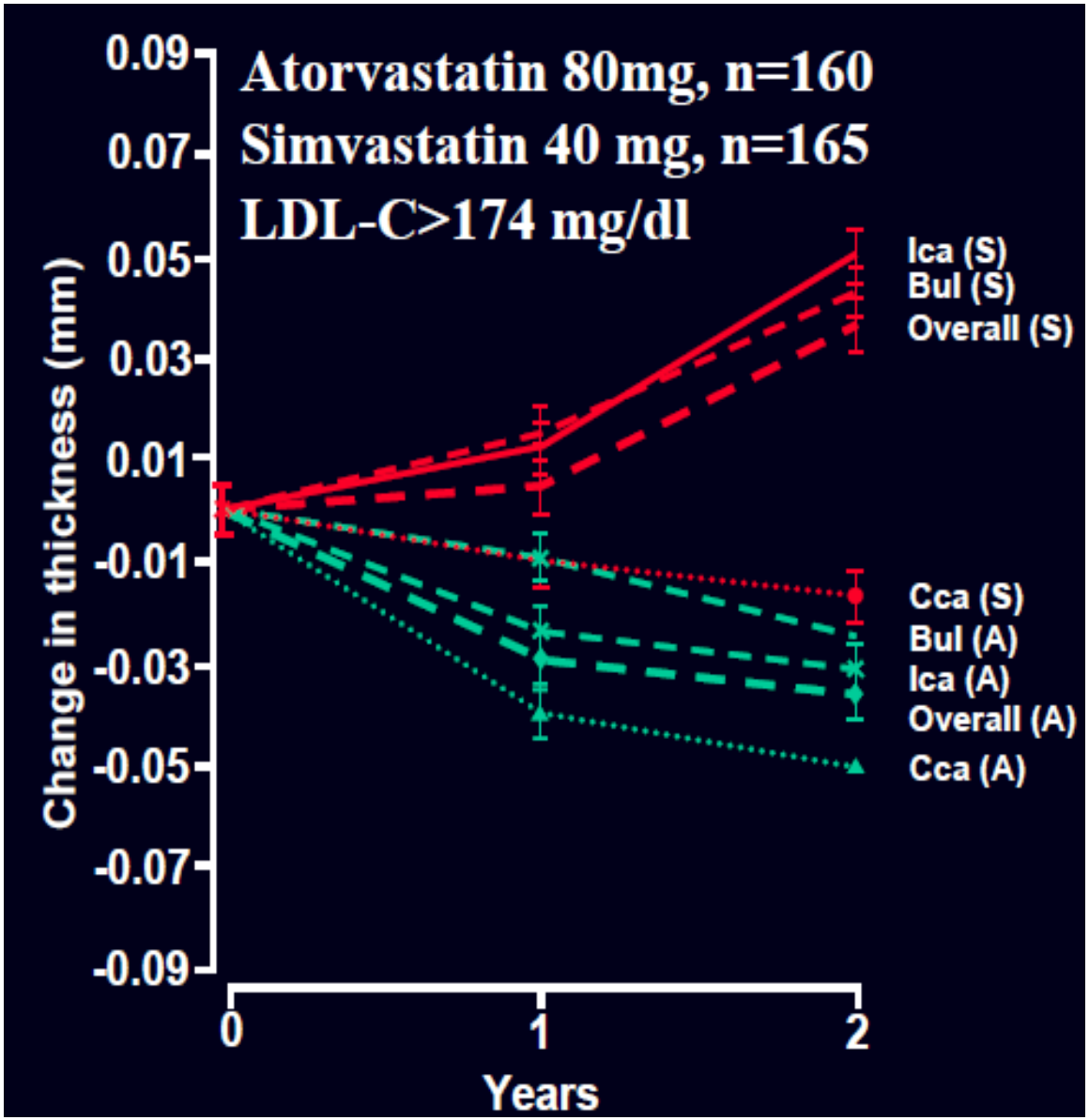
919 asymptomatic patients with early carotid atherosclerosis

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.

Circulation *1994;90:1679*

ASAP



Aggressive LDLcholesterol reduction was accompanied by regression of carotid intima media thickness in patients with familial Hypercholesterolemia whereas conventional LDL lowering was not.

Lancet 2001 Feb 24;357(9256):577-81

Summary of trials

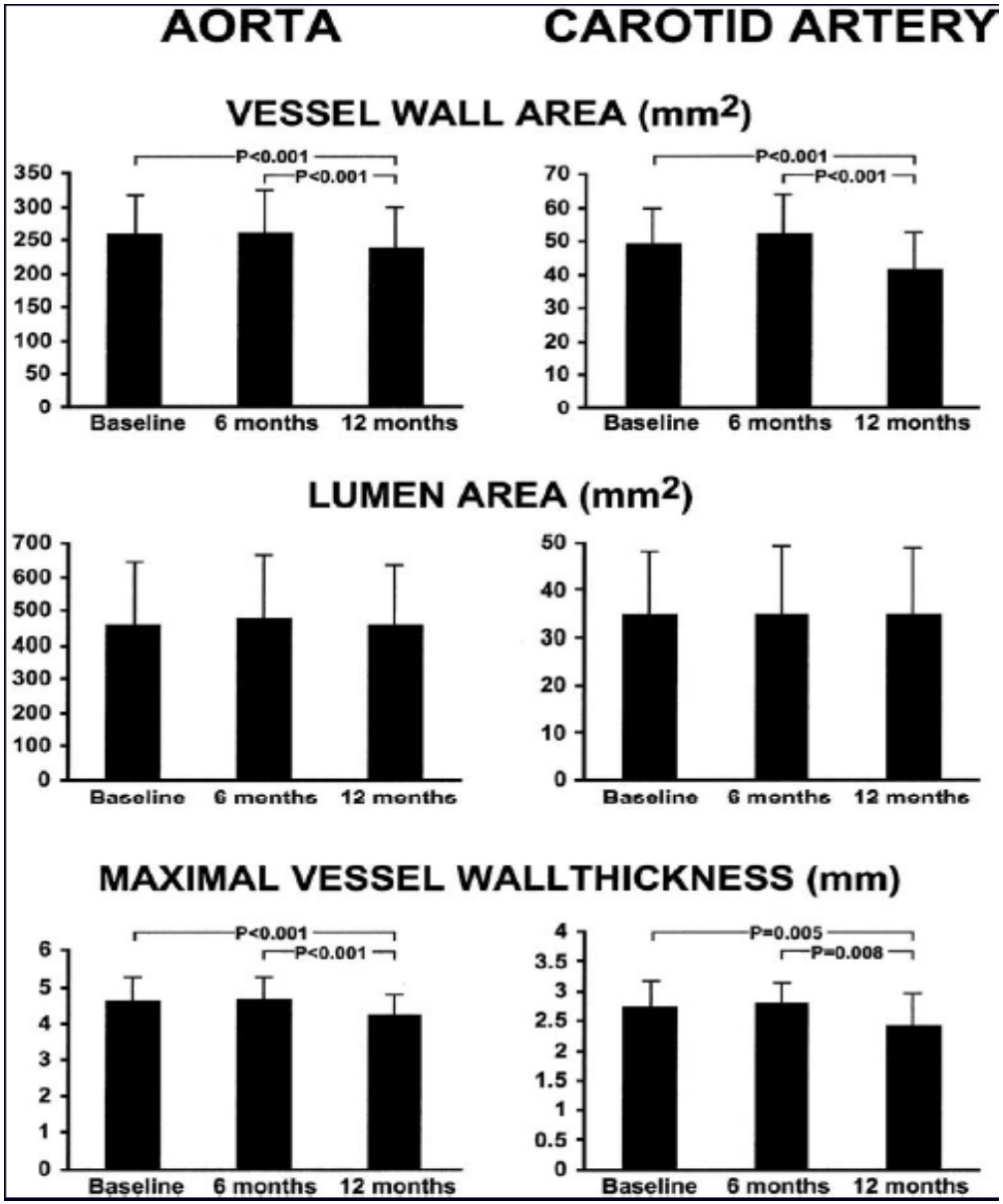
ACAPS	919/3	L20-40/Pl	IMT	-0.015
ARBITER1	161/1	A80/P40	IMT	-0.059
ASAP	325/2	A80/S40	IMT	-0.033
CAIUS	305/3	P40/Pl	IMT	-0.0132
ENHANCE		S80+E1/S80	IMT	0.0026
KAPS	424/3	P40/Pl	IMT	-0.014
LIPID	522/4	P40/Pl	IMT	-0.0155
METEOR	984/2	R40/Pl	IMT	-0.0145
ORION	43/2	R80/R5	Volume	No change
PLAC-II	151/3	P20-40/Pl	IMT	-0.0082
RADIANCE1	850/2	T60+A/A	IMT	-0.0006
RADIANCE2	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

Evidence of plaque regression

Aorta

Effects of Simvastatin on Atherosclerotic Lesions: **MRI Study**



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

Evidences of Plaque Regression Coronary Artery

REVERSAL

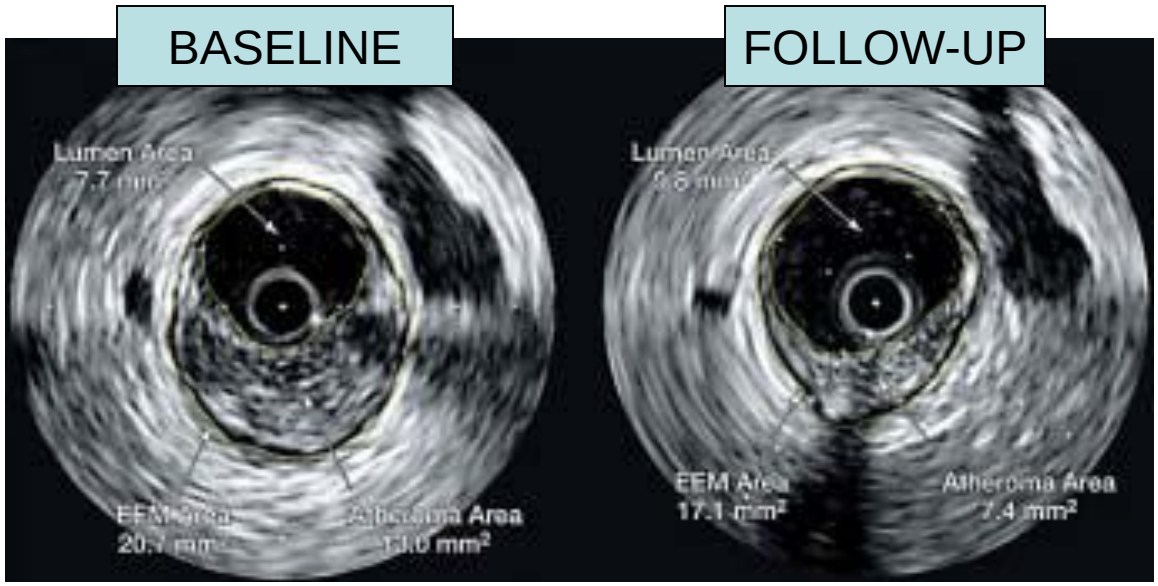
Double-blind period

654 patients

ATORVASTATIN 80 MG

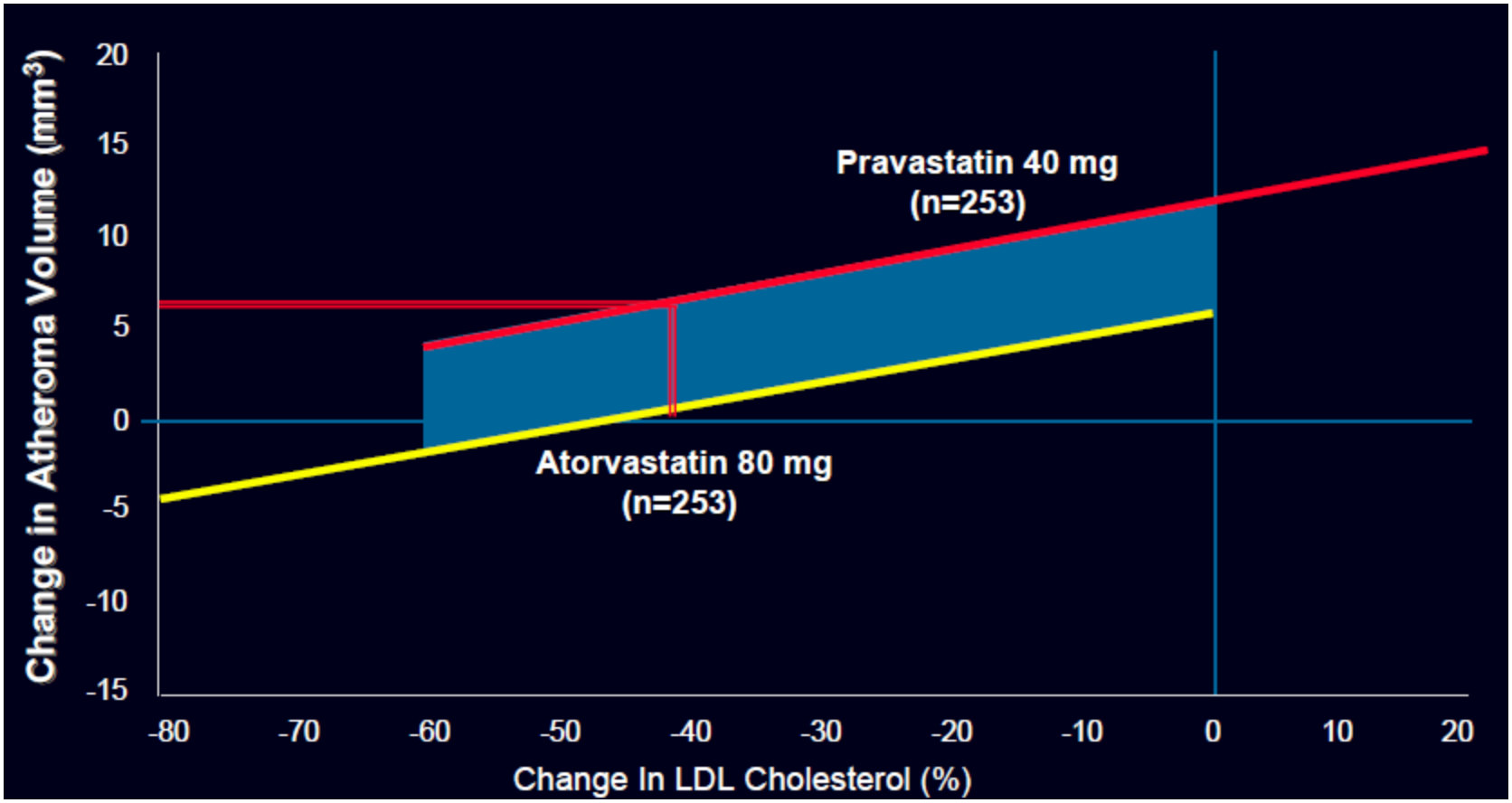
PRAVASTATIN 40 MG

18-month follow-up with IVUS



***JAMA* 2004;291:1071**

REVERSAL



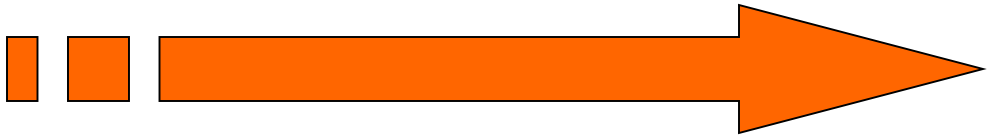
Intensive lipid-lowering treatment with atorvastatin reduced progression of coronary atherosclerosis compared with pravastatin. The progression rate at any level of LDL-C reduction was lower with atorvastatin compared with pravastatin.

ASTEROID

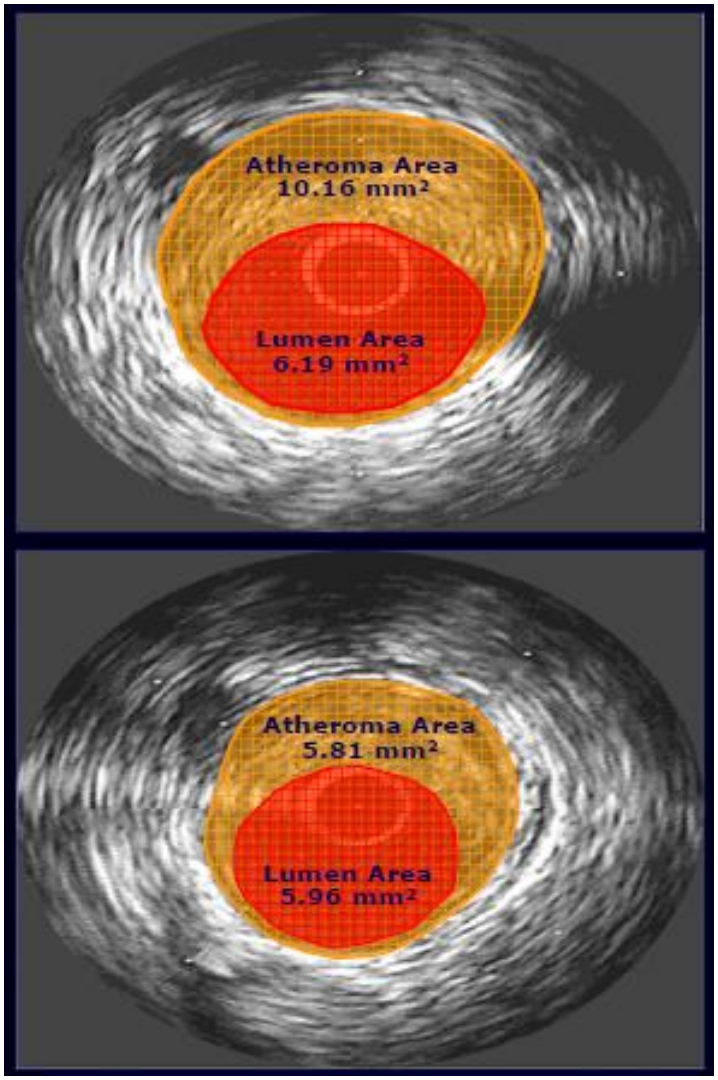
A Study To evaluate the Effect of Rosuvastatin On Intravascular ultrasound-Derived Coronary Atheroma Burden

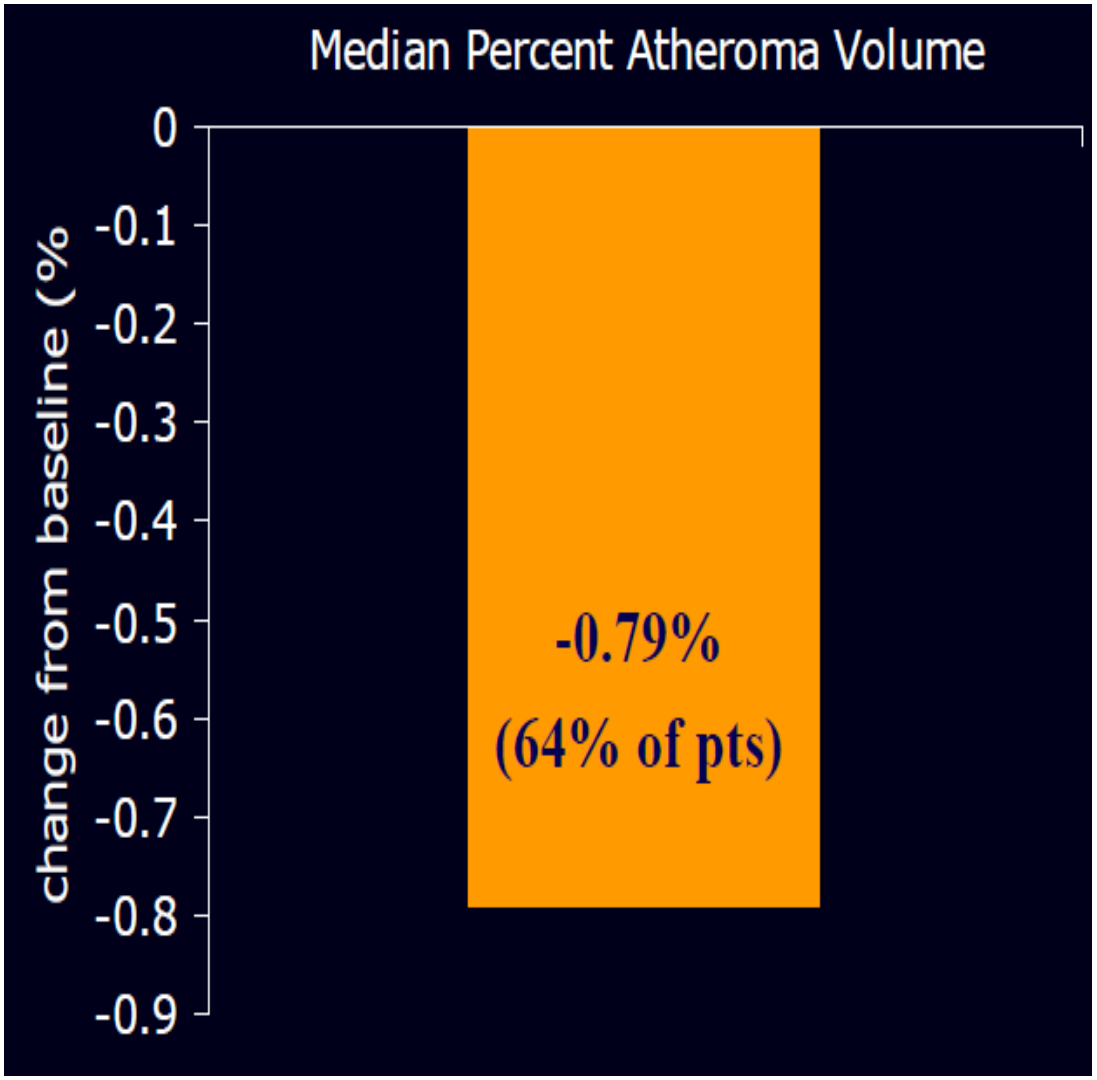
- Patients with CAD
- Undergoing coronary angiography
- Target coronary artery: ≤50%
- reduction in lumen diameter of ≥40 mm segment
- No cholesterol entry criteria
- ≥18 years

Rosuvastatin 40 mg
(n=349 evaluated serial IVUS examinations)



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

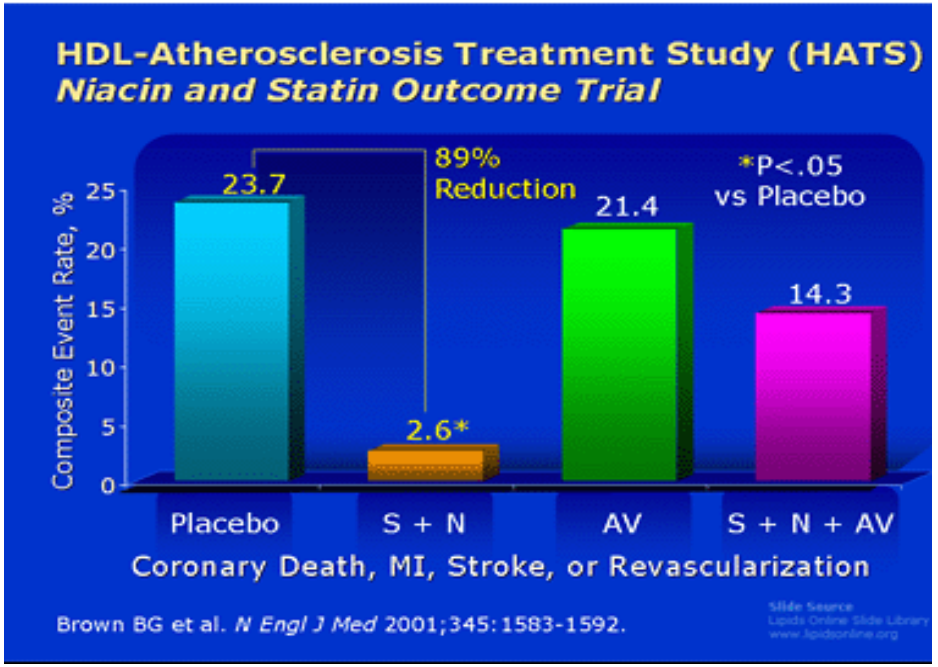




HATS Trial

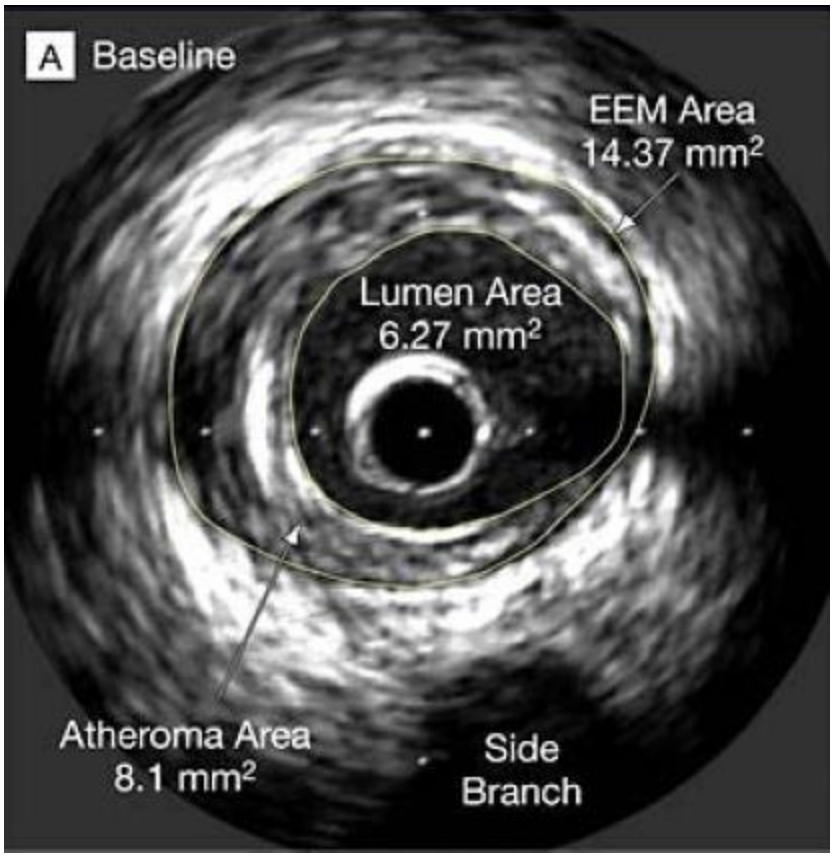
- Simvastatin plus niacin given to subjects with low levels of HDL cholesterol, elevated levels of LDL cholesterol and coronary disease .

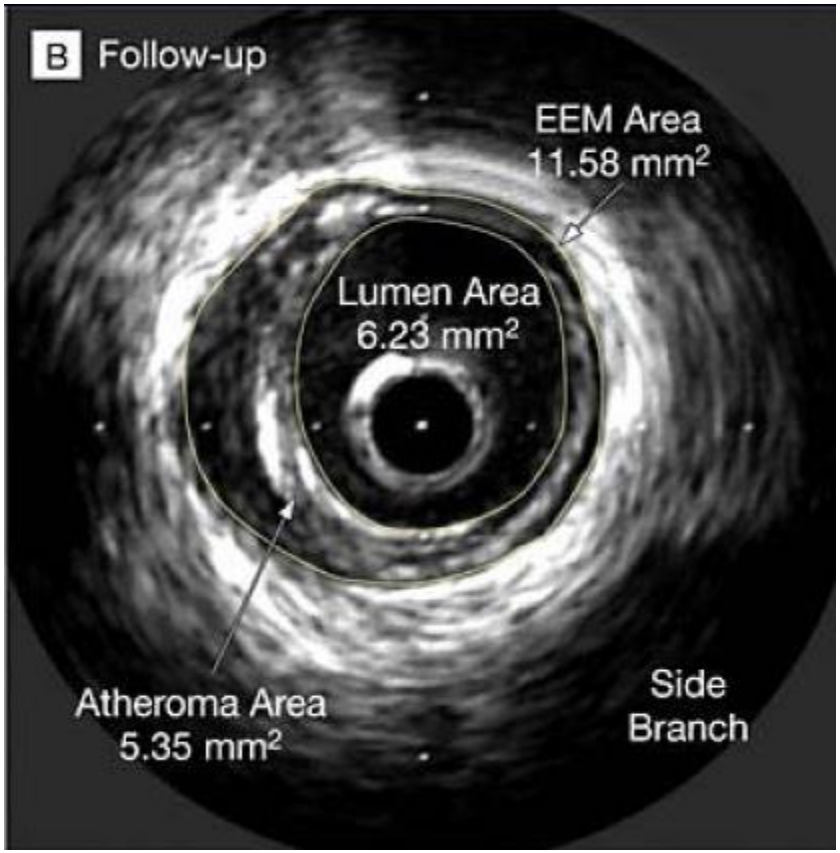
- A 0.4% decrease in angiographically detected stenosis and an 87% reduction in cardiovascular end points.



- LDL was lowered by 42% and HDL raised by 26%.

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





-14.1mm3 or a 4.2% decrease from baseline

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

JAMA2003:290:2292

Novel interventions being tested in clinical & preclinical trials

- Non-statin LDL lowering therapies

1. Cholesterol absorption inhibitors
2. ACAT inhibitors
3. MTP inhibitors
4. Antisense oligonucleotide against apo B-100
5. PCSK-9 inhibitors

- New HDL based therapies

1. Niacin-laropiprant inhibitors
2. Fibrates
3. CETP inhibitors
4. Small molecule stimulator of apoA-1 gene transcription
5. Reinfusion of ex-vivo delipidated endogeneous HDL
6. Apo A-1 mimetic peptides
7. IV infusion of human plasma derived wild type apo A-1
8. Endothelial lipase inhibitors

Predictors of plaque regression

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

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

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

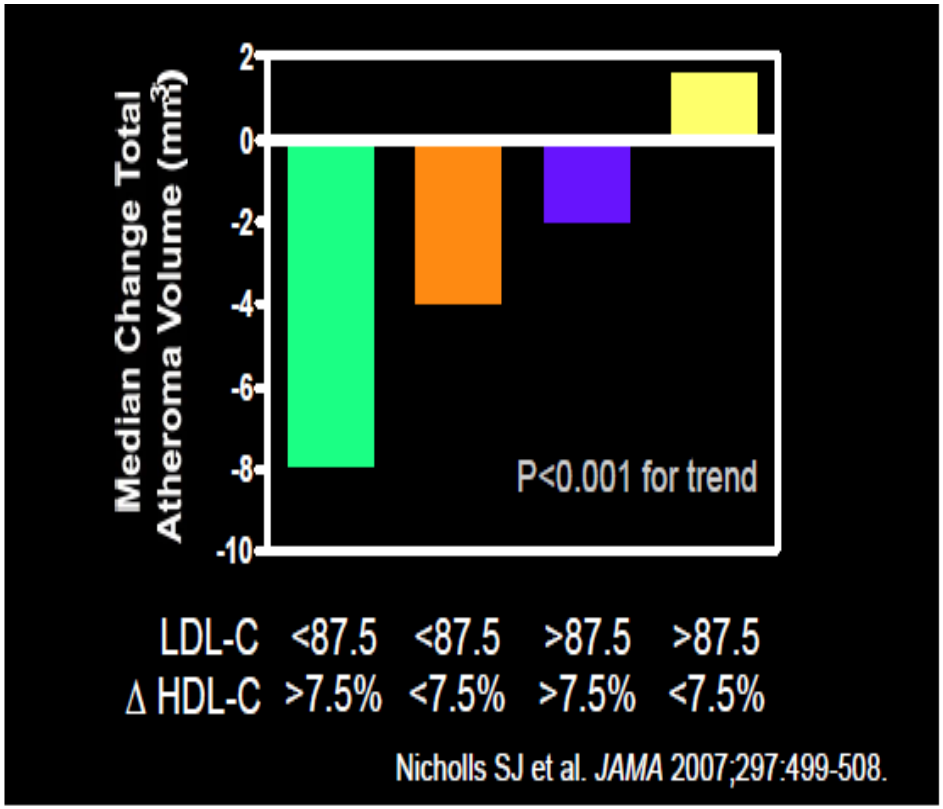
  The SANDS randomised trial

A post-hoc analysis of 4 prospective randomized trials was performed by Nicholls et al.in 2007

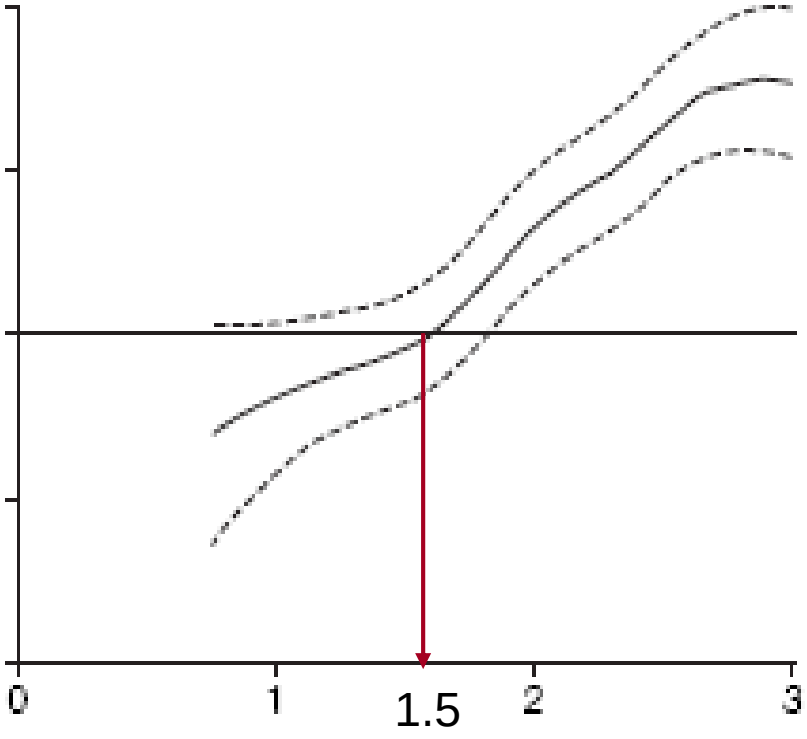
- Mean (SD) decrease in total atheroma volume of 2.4 (23.6) mm3 (P<.001) during statin therapy
- Significant decrease in LDL-C as well as significant increase in HDL-C.
- Mean levels and treatment-mediated changes in LDL-C, total cholesterol, non-HDL cholesterol, apolipoprotein B, and ratio of apolipoprotein B to apolipoprotein A-I were significantly correlated with the rate of atherosclerotic progression
- Changes in HDL-C were inversely correlated with atheroma progression.
- **In multivariate analysis, substantial atheroma regression (≥5% reduction in atheroma volume) was observed in patients with levels of LDL-C less than the mean (87.5 mg/dL) during treatment and percentage increases of HDL-C greater than the mean (7.5%; P<.001).**

substantial atheroma regression (≥5% reduction in atheroma volume) was observed in patients

with levels of LDL-C <87.5 mg/dL



Ratio of LDL-C:HDL-C <1.5



Lifestyle modification and atherosclerosis regression

- Stearic acid , a saturated fatty acid appeared to significantly protect against atherosclerosis progression.
- Both energy intake and physical exercise, mediated through BMI, may be notably important lifestyle factors for progression of atherosclerosis.
- Quitting a l0-cigarette/d habit would yield a predicted 0.033-mm/y reduction in the annual rate of carotid IMT.
- The most protective lifestyle change was 5-kg/m2 reduction in BMI which was associated with a 0.065-mmly reduction in the annual rate of carotid IMT progression.
- Reduction in dietary cholesterol intake by 100 mg/d would yield a predicted 0.028-mm/y reduction in the annual rate of carotid IMT progression.

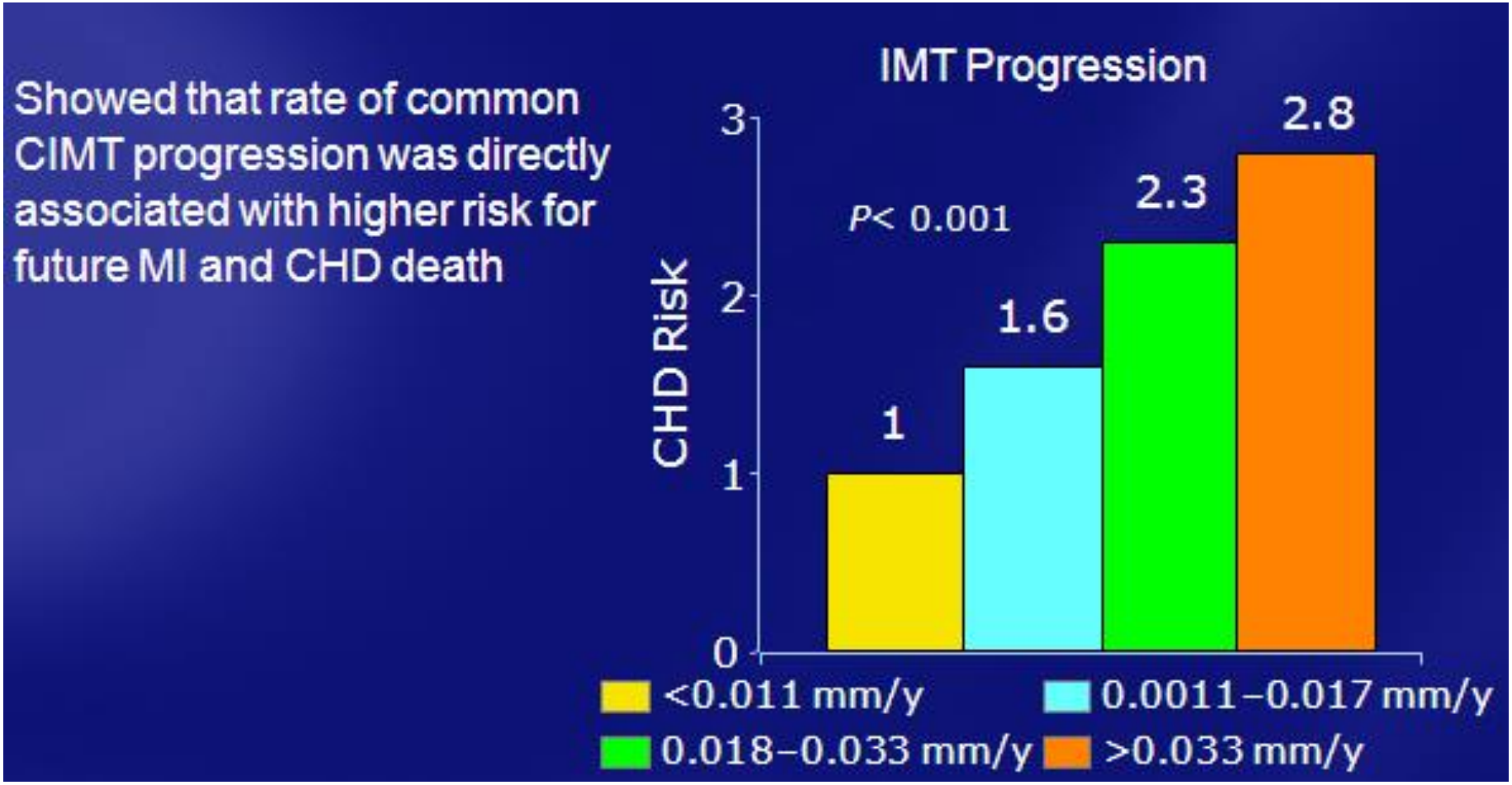
- *However change in alcohol consumption was not found to be effective in plaque regression. This results corroborate the results reported by the ARIC study, which found no association between current alcohol intake and carotid atherosclerosis .*

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

CIMT Progression Rate: Marker of Increased Risk for Events

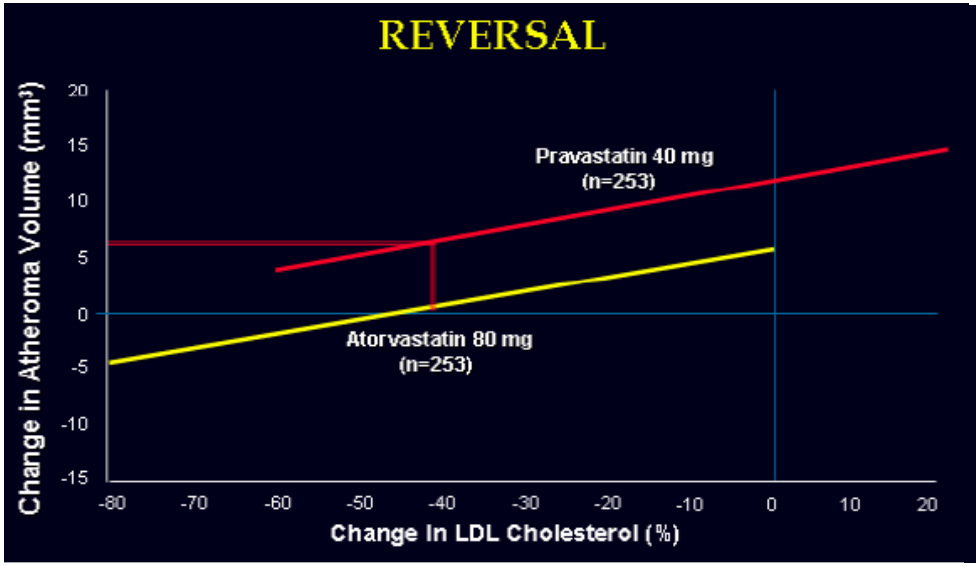
CLAS: Secondary Prevention, Men, Colestipol/Niacin vs Placebo

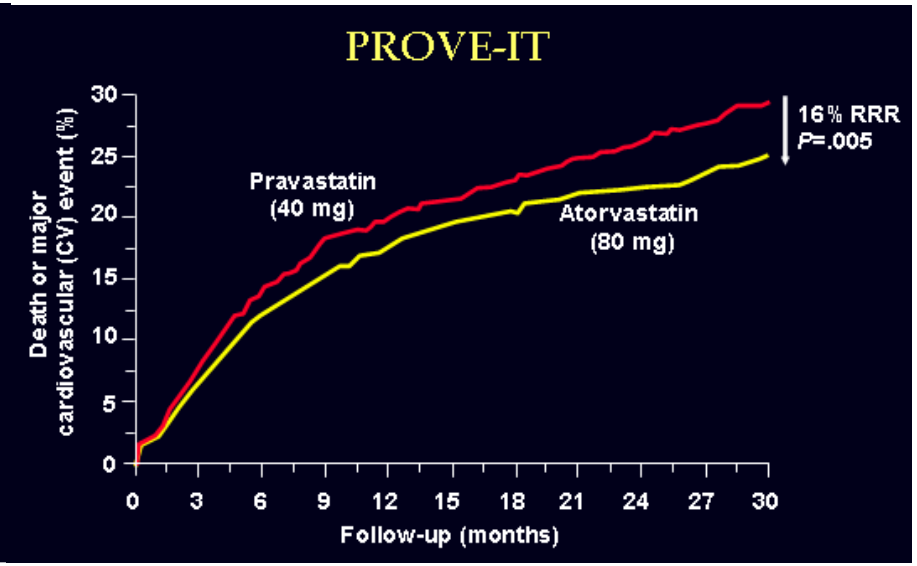
Showed that rate of common CIMT progression was directly associated with higher risk for future MI and CHD death



Hodis HN et al. *Ann Intern Med* 1998;128:262-269.

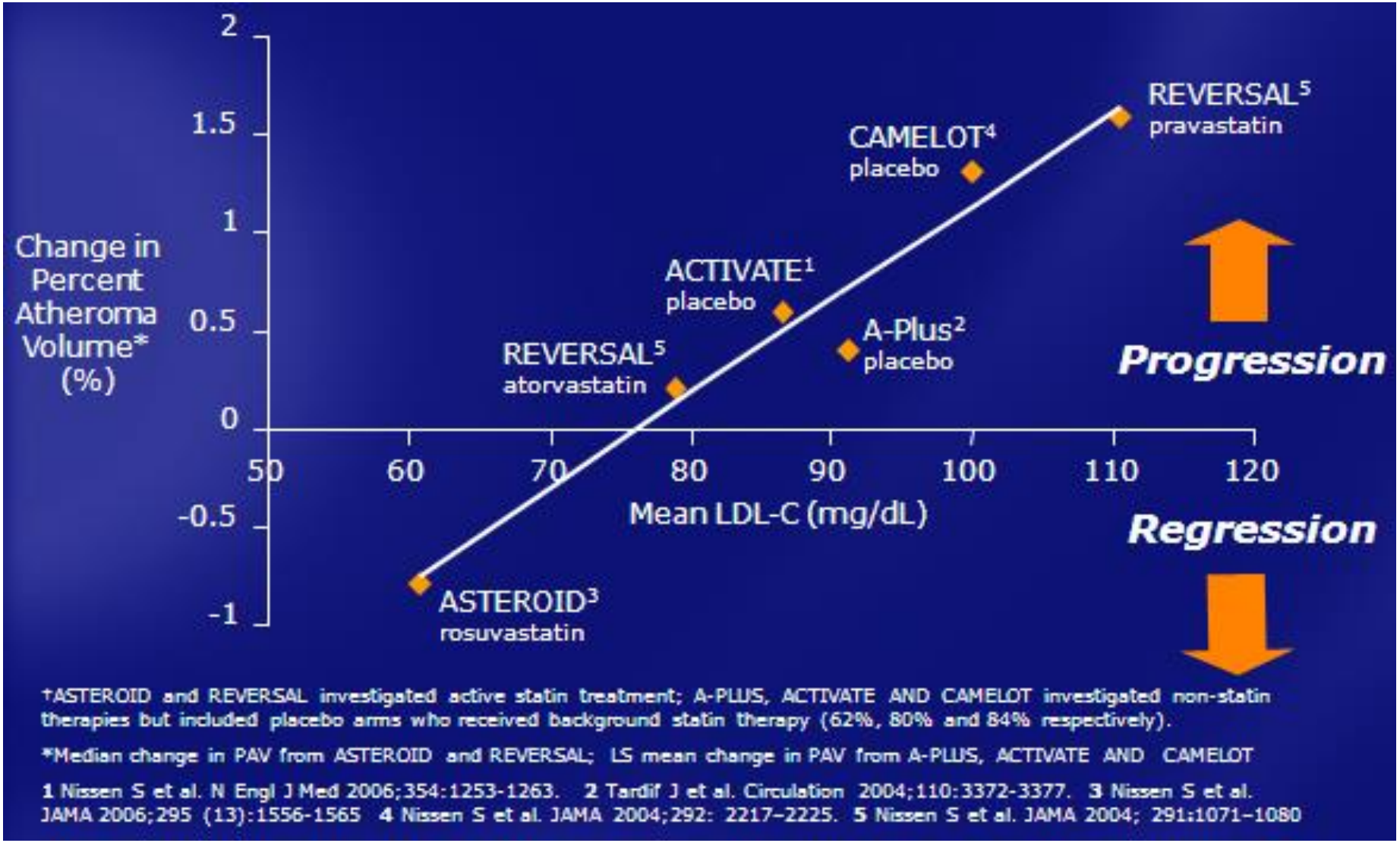
Association between Coronary Plaque Progression as Measured by IVUS & CV Events





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 Relationship Between Mean LDL-C and Change in Percent Atheroma Volume (PAV) in IVUS Studies



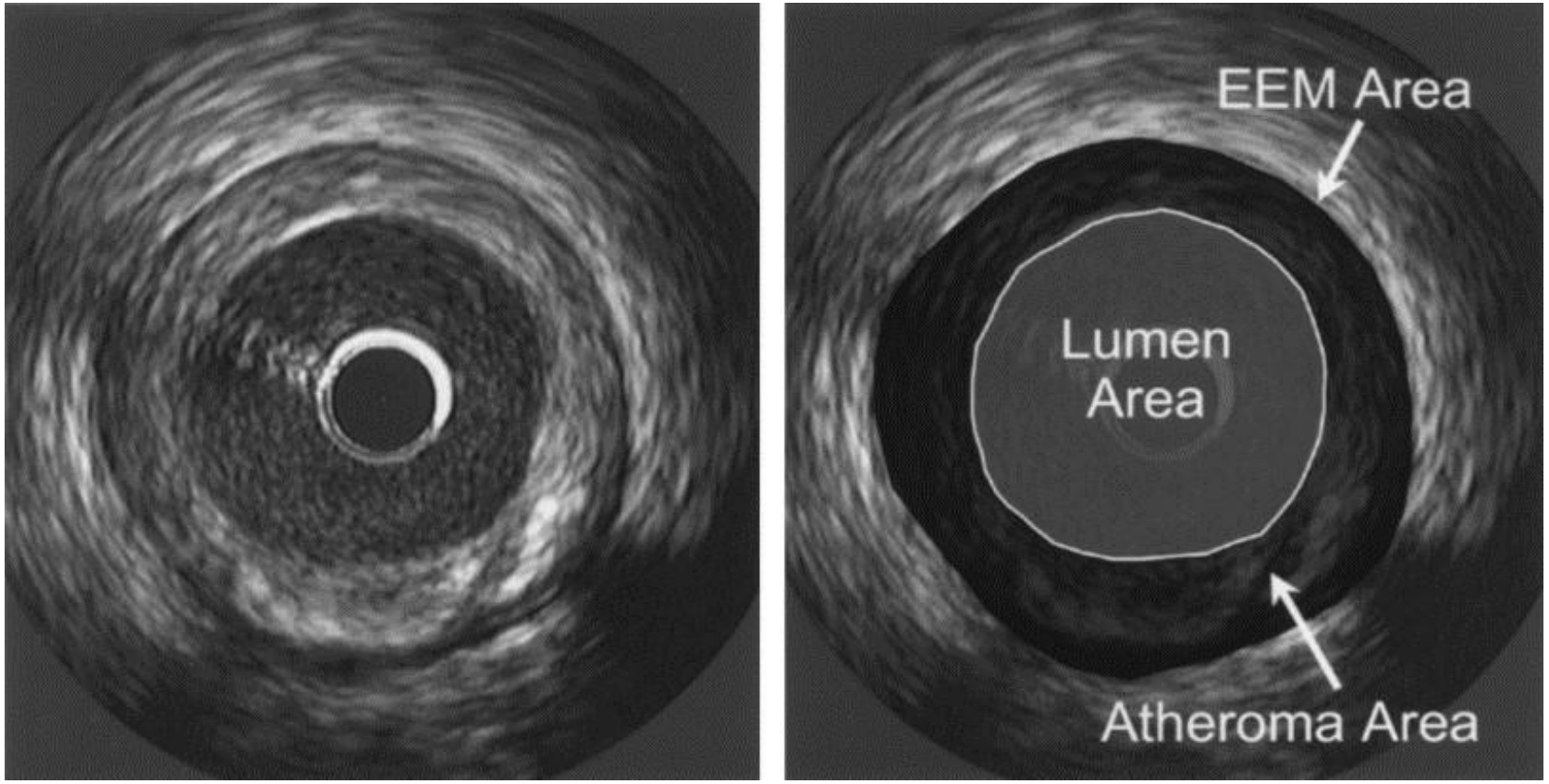
†ASTEROID and REVERSAL investigated active statin treatment; A-PLUS, ACTIVATE AND CAMELOT investigated non-statin therapies but included placebo arms who received background statin therapy (62%, 80% and 84% respectively).

*Median change in PAV from ASTEROID and REVERSAL; LS mean change in PAV from A-PLUS, ACTIVATE AND CAMELOT

1 Nissen S et al. N Engl J Med 2006;354:1253-1263. **2** Tardif J et al. Circulation 2004;110:3372-3377. **3** Nissen S et al. JAMA 2006;295 (13):1556-1565 **4** Nissen S et al. JAMA 2004;292: 2217–2225. **5** Nissen S et al. JAMA 2004; 291:1071–1080

IVUS measurements

- TAV =EEM_{CSA}-$LUMEN_{CSA}$
- PAV= average atheroma area/average EEM area

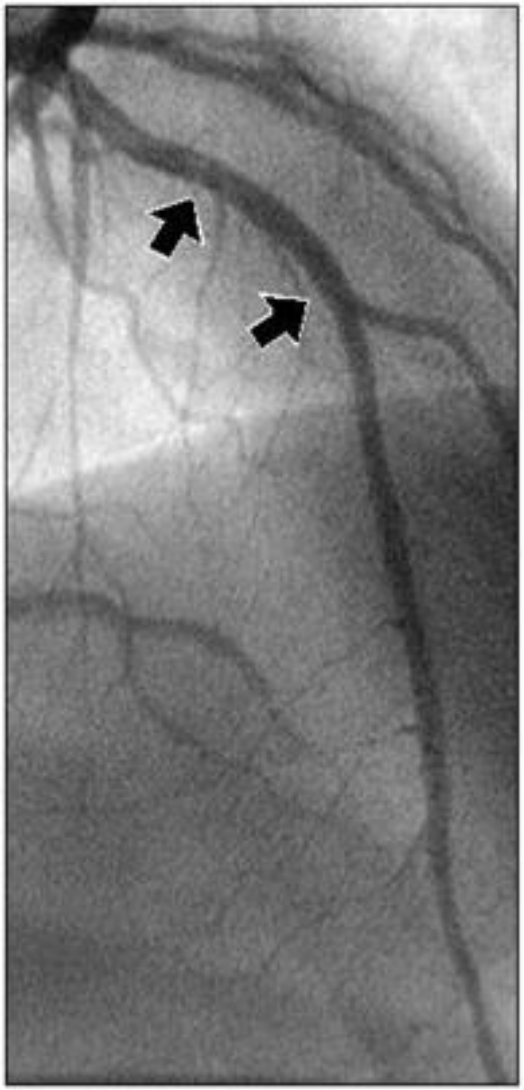


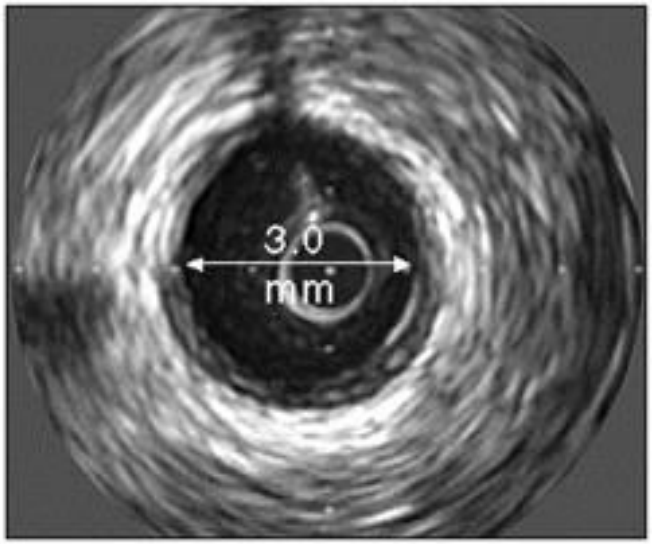
total atheroma volume (TAV) ;percent atheroma volume (PAV) ;external elastic membrane (EEM) cross-sectional area (CSA)

The IVUS Technique Can Detect Angiographically 'Silent' Atheroma

Angiogram

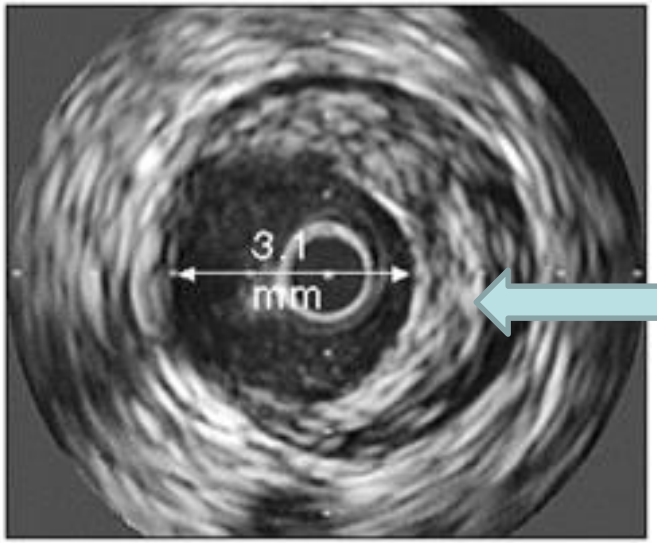
No evidence of disease





IVUS

Little evidence of disease

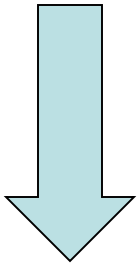


Atheroma

Pitfall of PAV

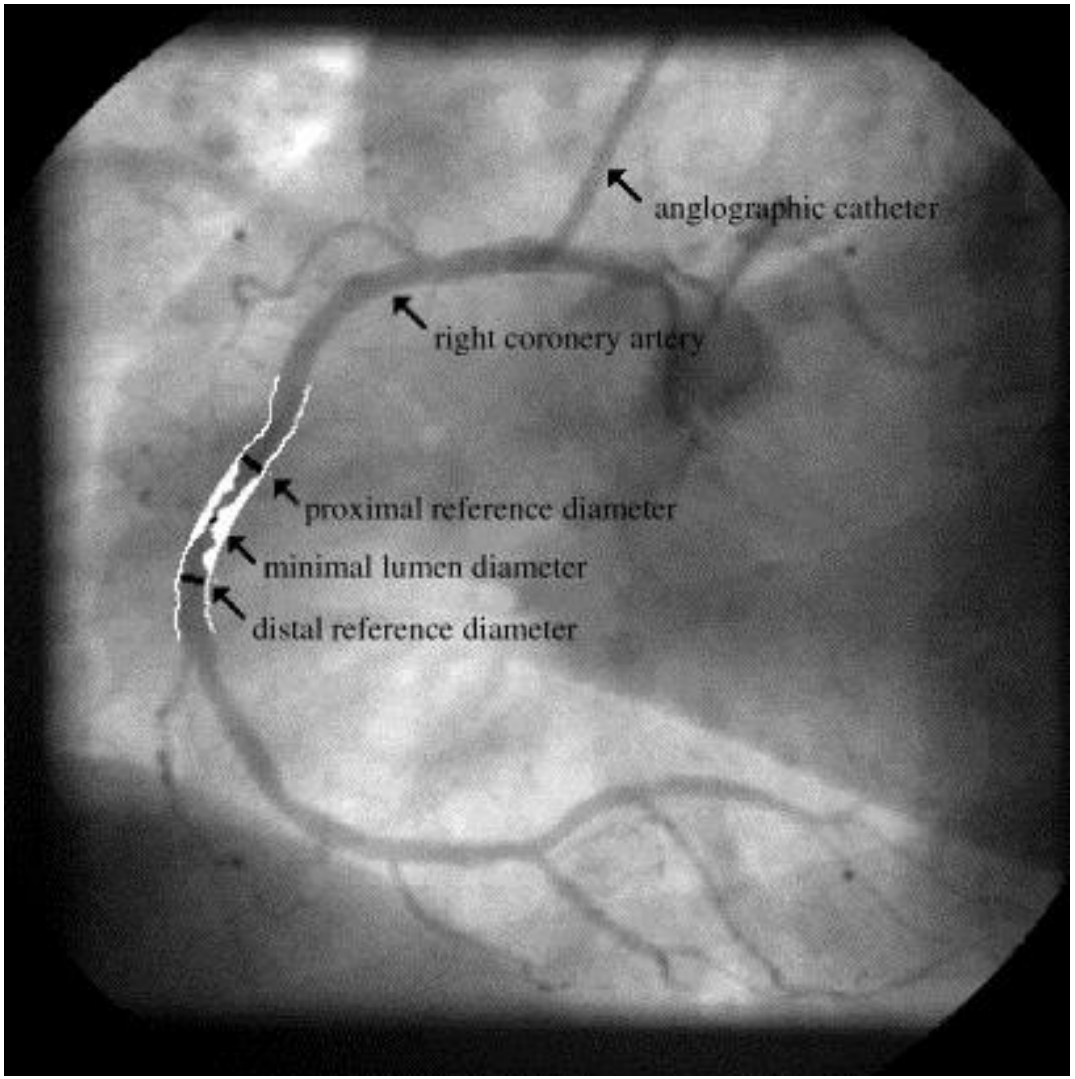
5% increase of atheroma volume &

10% increase in EEM(positive remodelling)



~4.5% decrease in PAV (percent atheroma volume)

‘Angiographic Paradox’



‘Angiographic Paradox’
Plaque quantity vs quality

- Large trials of lipid lowering have shown statistically significant angiographic evidence of regression.

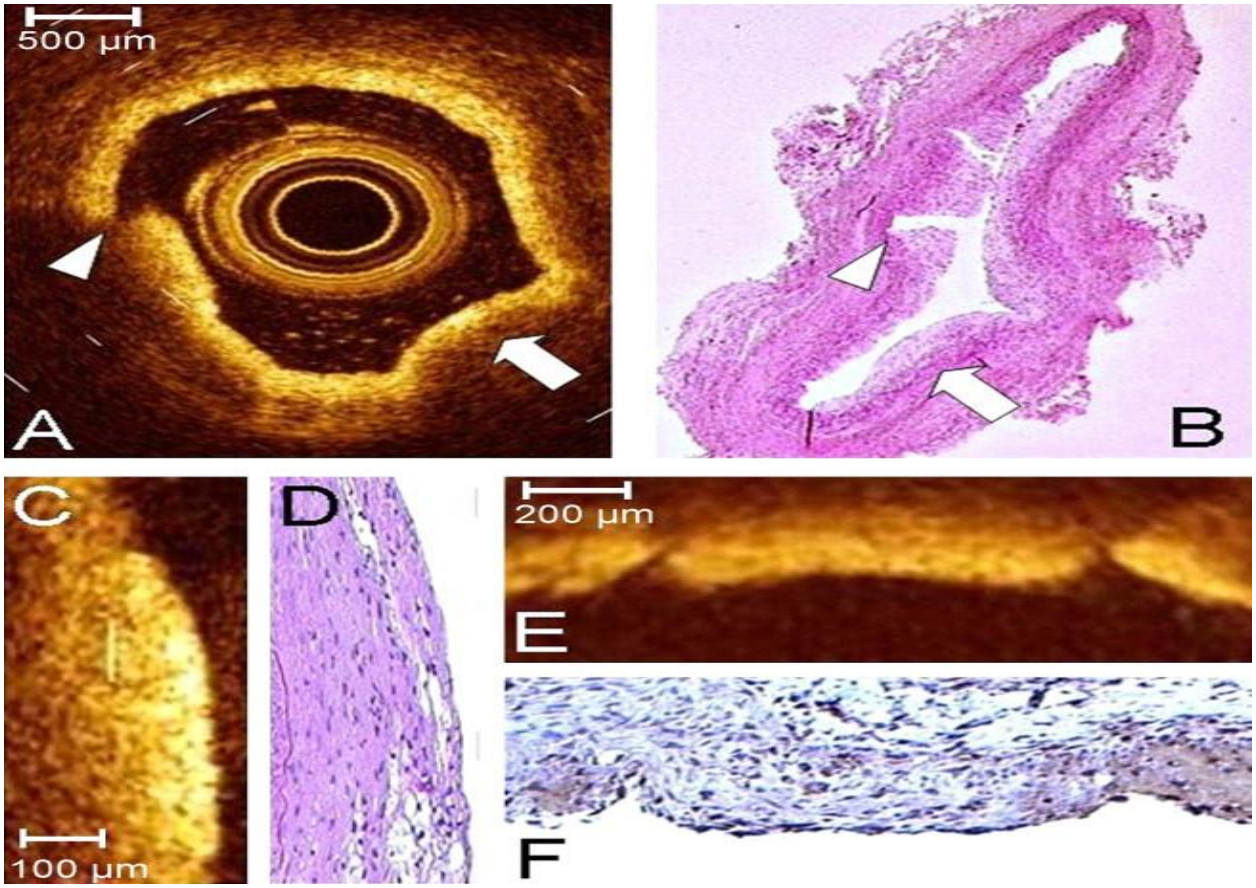
- *However, reductions in clinical events were surprisingly small.*

- Lipid-rich, vulnerable plaques have a central role in acute coronary syndromes. They are generally full of intracellular and extracellular lipid, rich in macrophages and tissue factor, have low concentrations of smooth muscle cells, and usually have only a thin fibrous cap under an intact endothelial layer

But vulnerable plaques are usually small in size and cause less than 50% occlusion.

Optical Coherence Tomography Imaging

OCT can provide sufficient resolution of atherosclerotic plaques to near histological level and detailed spatial structure of the artery.



- All fibrous plaques, macrocalcifications and echolucent regions identified by IVUS are visualized in corresponding OCT images.

- Intimal hyperplasia and echolucent regions, which may correspond to lipid pools, are identified more frequently by OCT than by IVUS.

J Am Coll Cardiol. 2002;39(4):604-609.

Unanswered Questions

- **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.**

Take Home Message

- Several animal experiments and clinical trials have proved beyond doubt that atherosclerosis is at least partially reversible.
- Reduction of cholesterol influx by aggressively lowering plasma LDL &/or enhancement of cholesterol efflux (‘reverse’ lipid transport) can reduce plaque burden.
- Lifestyle modification can influence plaque regression
- Newer imaging modalities (IVUS, OCT,etc.) are effective in serial assesment of plaque size