Arterial Wall Remodeling in Response to Atheroma Regression with Very Intensive Lipid Lowering

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THE UNIVERSITY OF ADELAIDE AUSTRALIA

SUB CRUCE LUMEN

Pathobiology

- plaque composition
- arterial wall remodeling

Vessel Wall Imaging

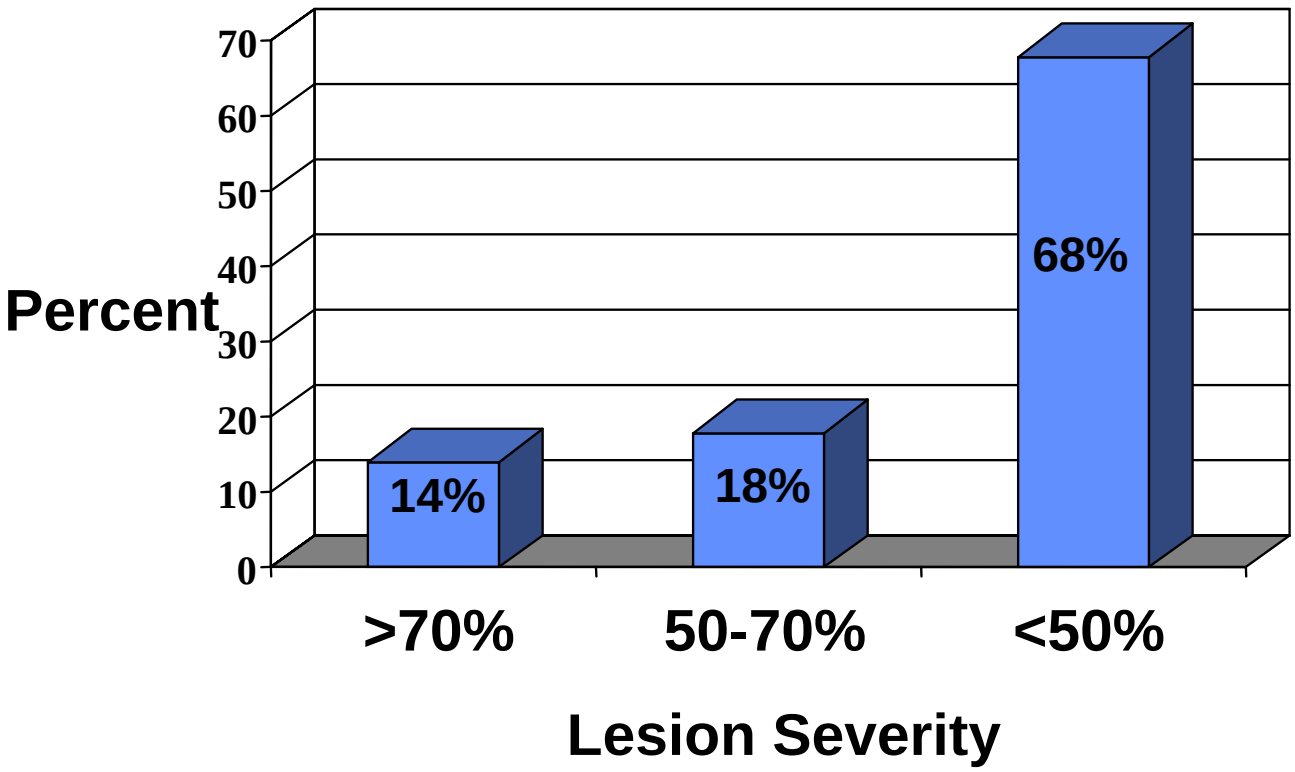
- ultrasound
- newer techniques

Effects of therapy

- LDL-C
- newer targets?

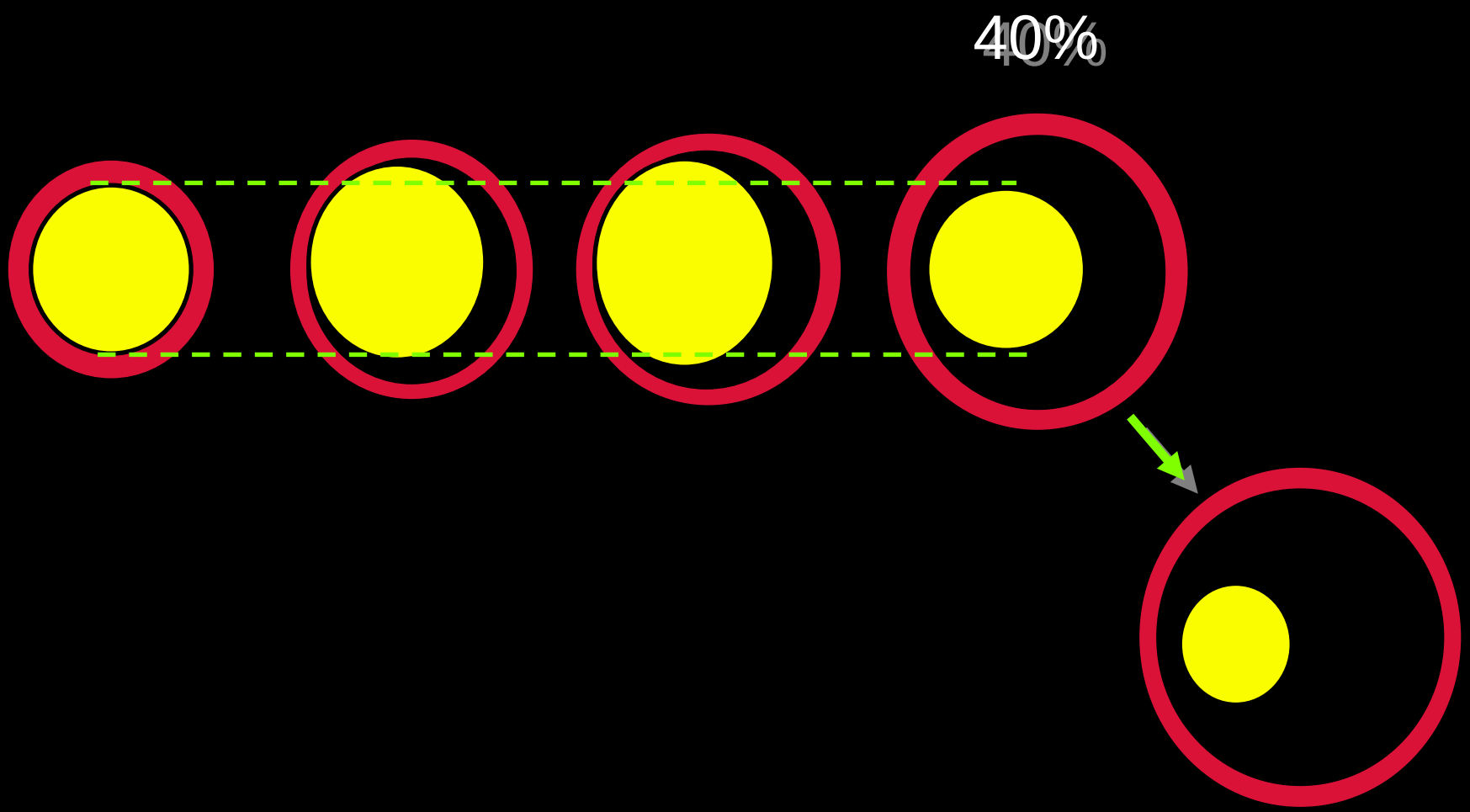
- Pathobiology
- Vessel wall Imaging
- Effects of Statins

Severity of Coronary Plaques before MI



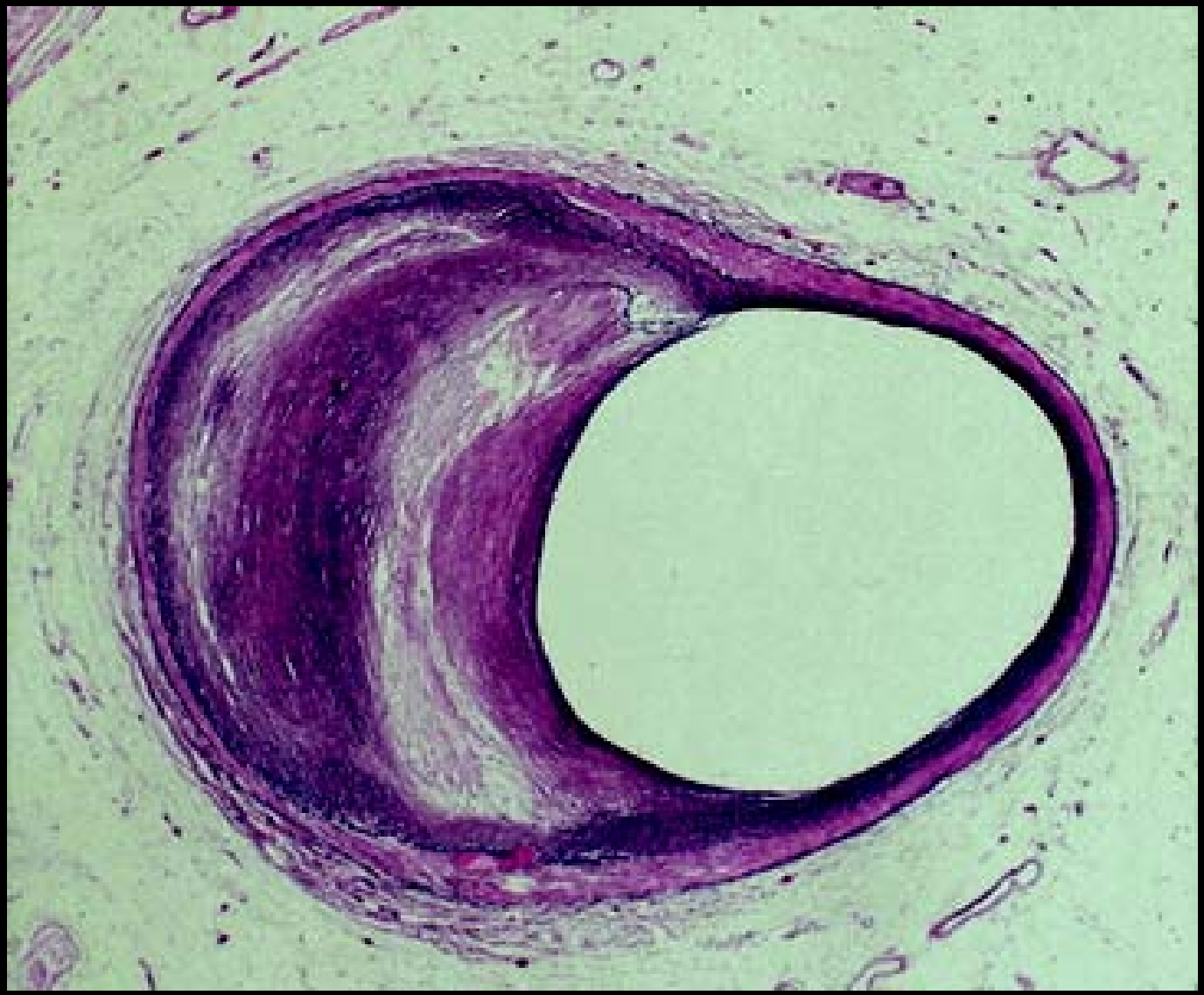
Ambrose et al. *J Am Coll Cardiol* 1988;12:56-62
Little et al. *Circulation* 1988;78:1157-66
Nobuyoshi et al. *J Am Coll Cardiol* 1991;18:904-10
Giroud et al. *Am J Cardiol* 1992;62:729-32

Arterial Remodeling



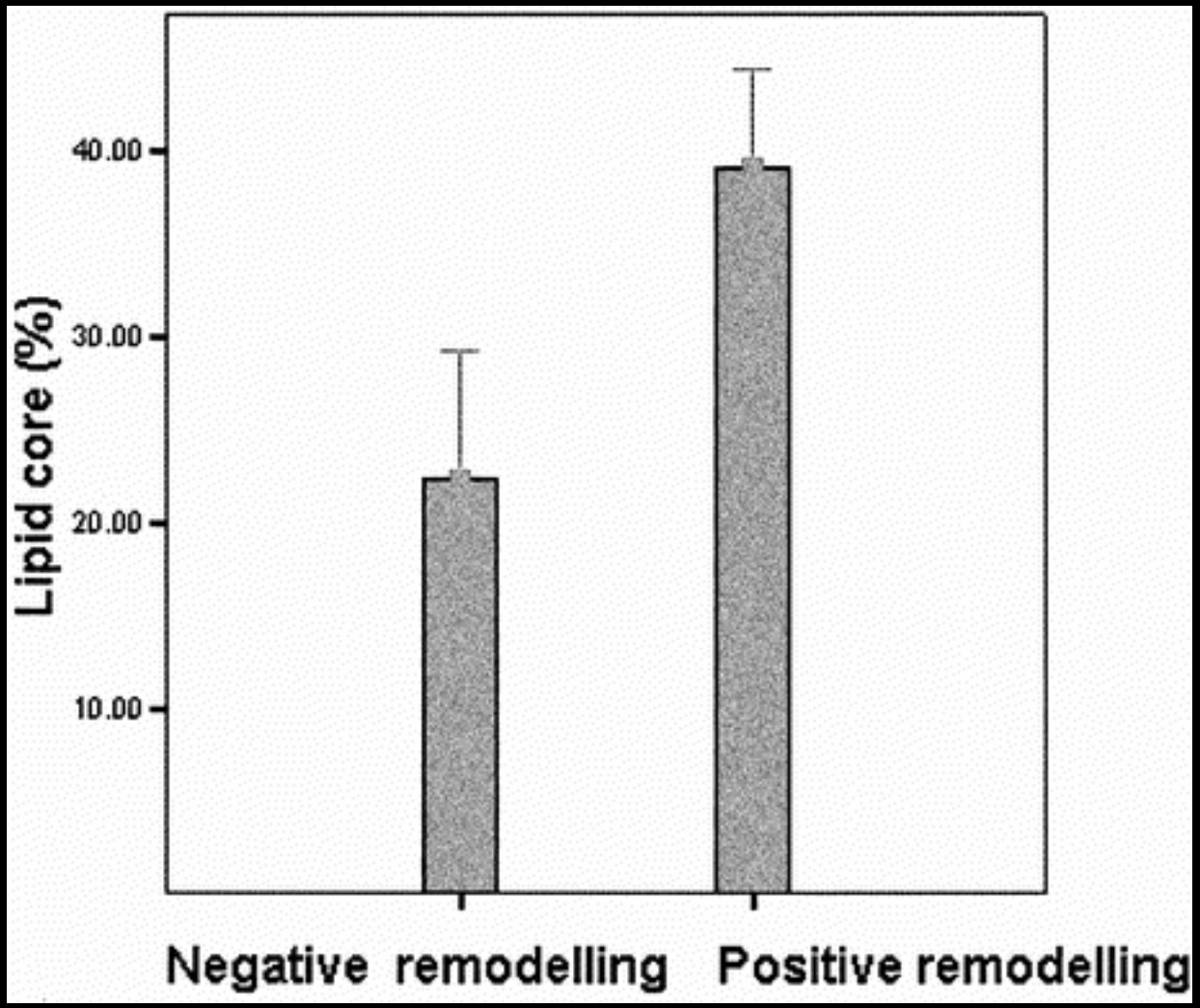
Glagov S et al. *N Engl J Med* 1987;316:1371-5

Arterial Remodeling



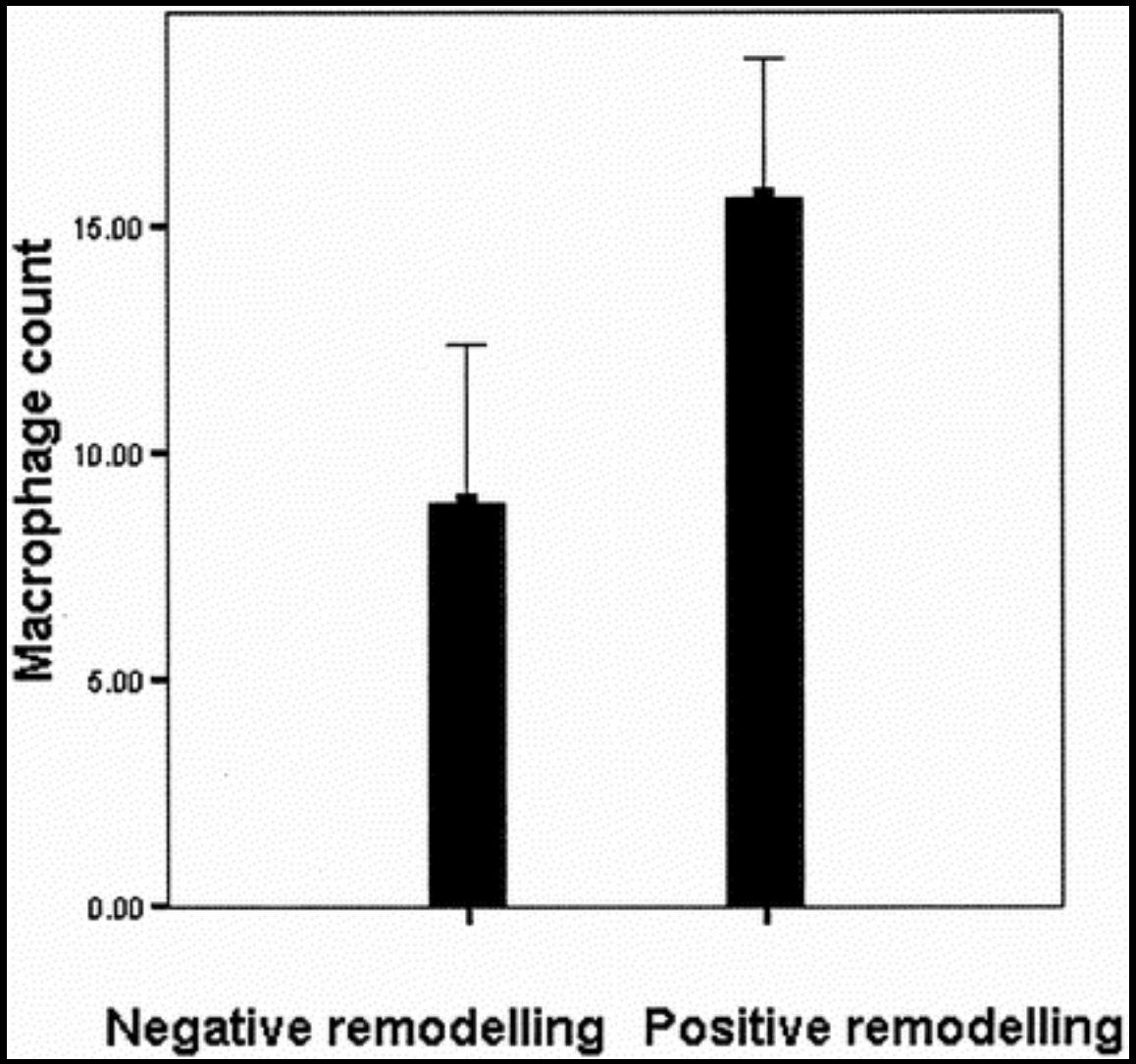
Varnava AM et al. *Circulation* 2002;105:939-43

Arterial Remodeling



Varnava AM et al. *Circulation* 2002;105:939-43

Arterial Remodeling

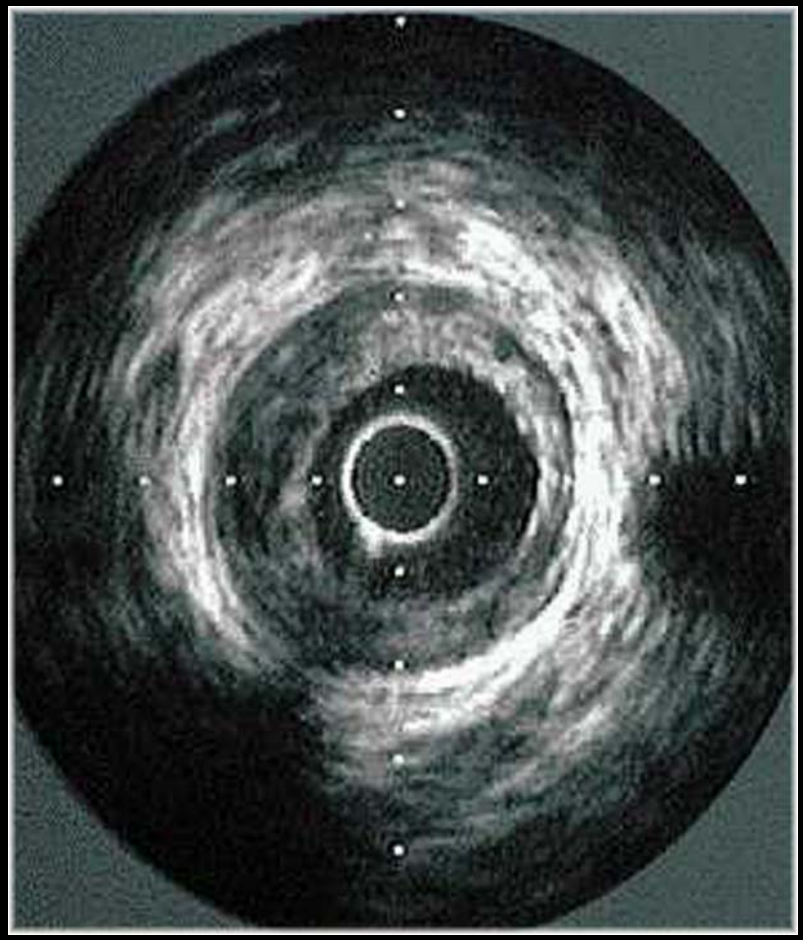


Varnava AM et al. *Circulation* 2002;105:939-43

- Pathobiology
- Vessel Wall Imaging
- Effects of Statins

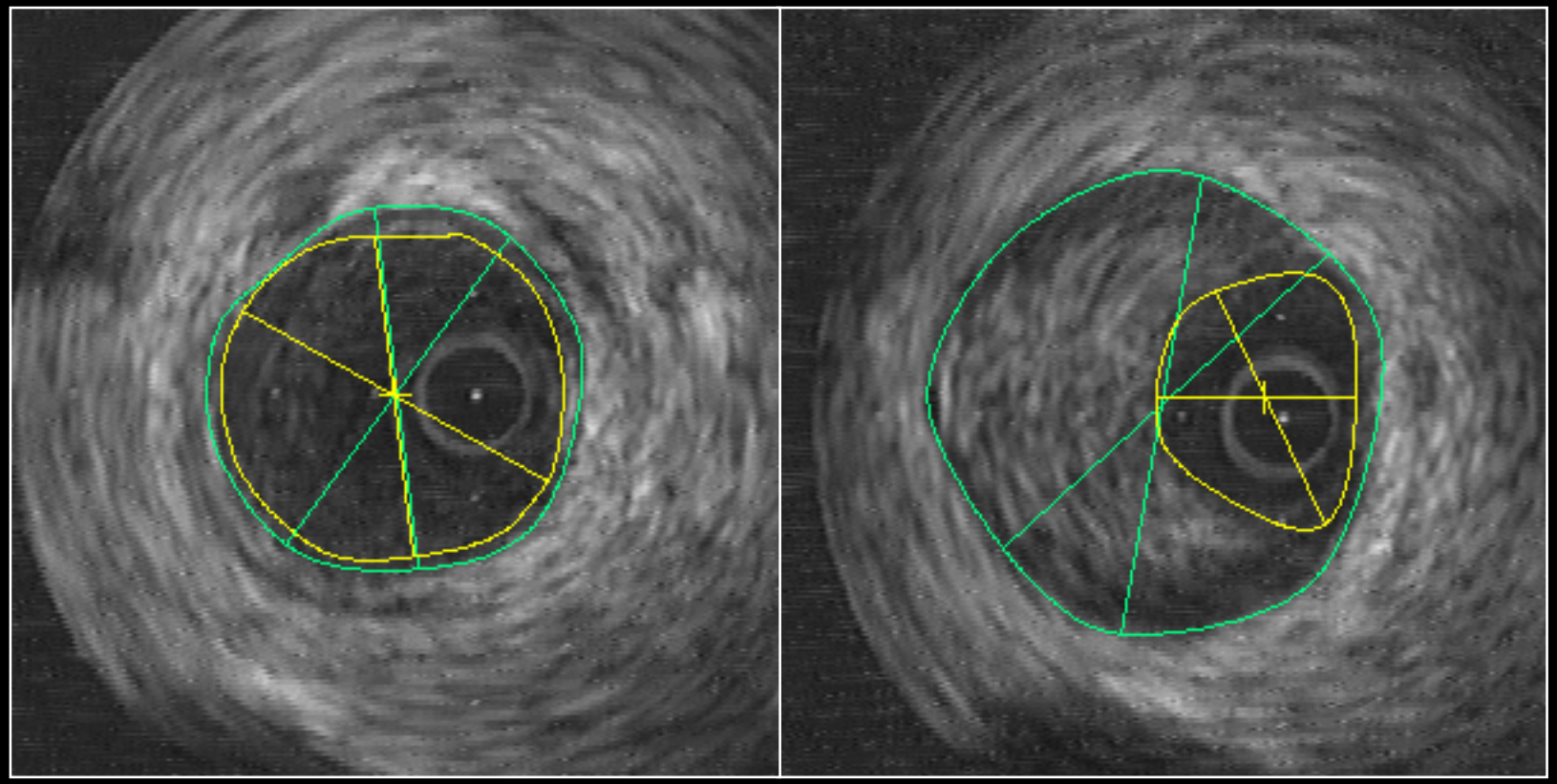
IVUS: Coronary Imaging

Fibrous Plaque



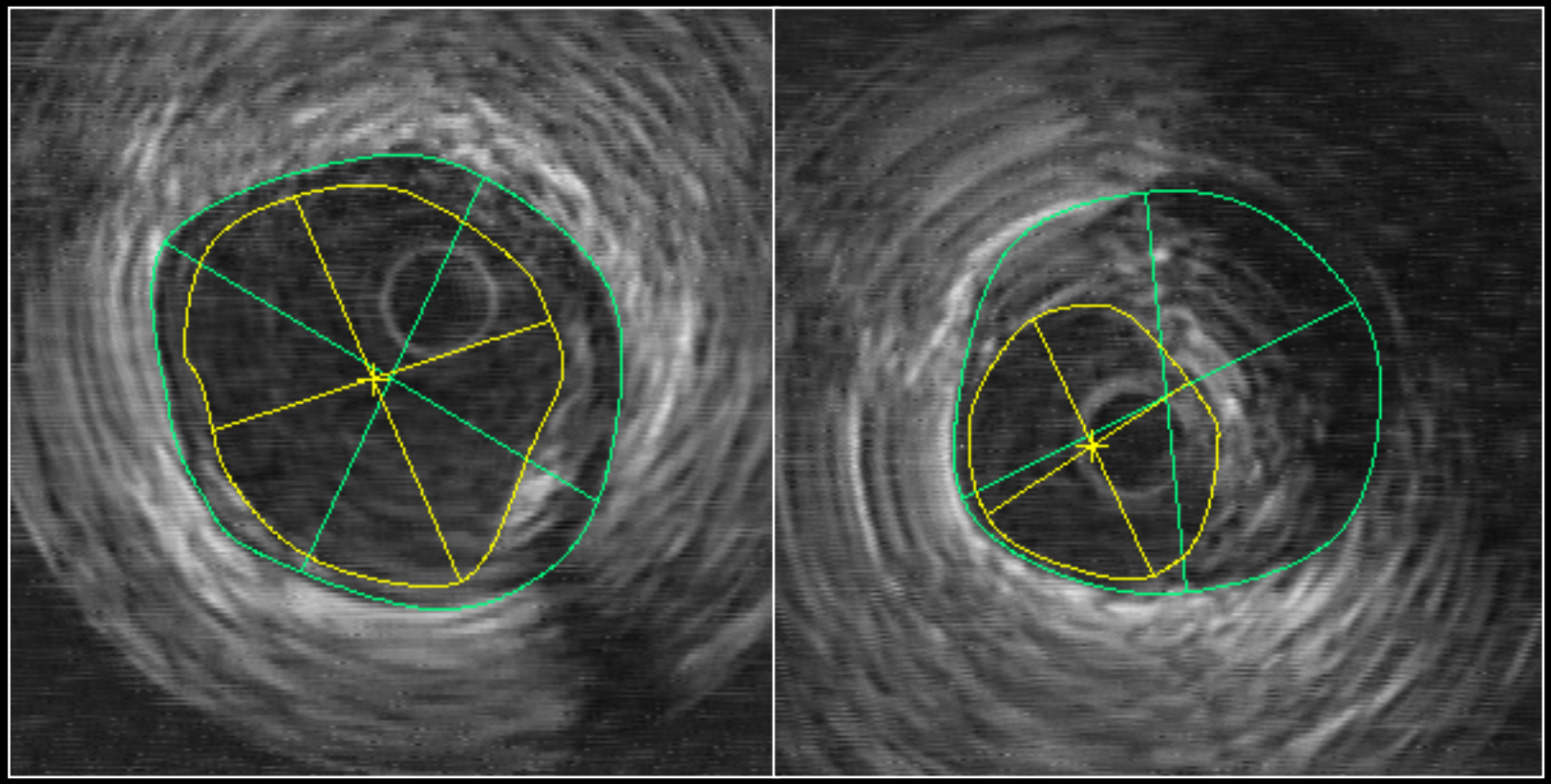
“Soft” Plaque

Positive Remodeling by IVUS



Worthley SG et al. *J Invasive Cardiol* 2006;18:28-31

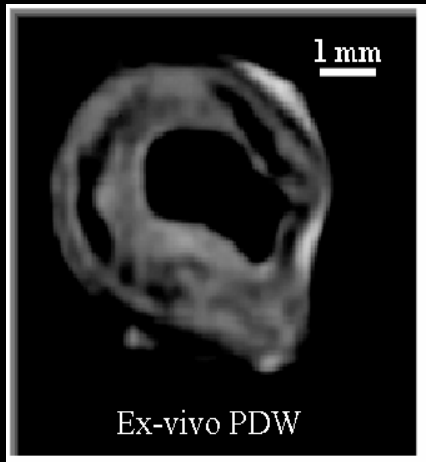
Negative Remodelling by IVUS

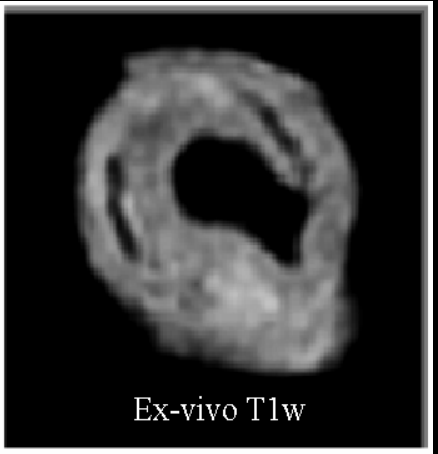


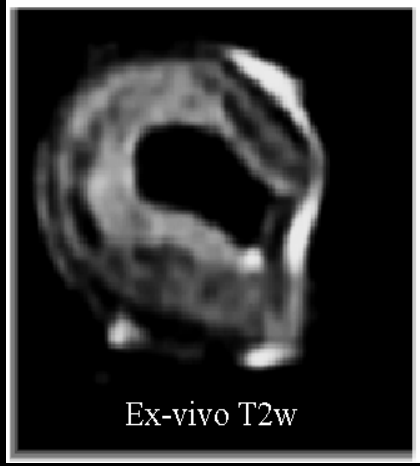
Worthley SG et al. *J Invasive Cardiol* 2006;18:28-31

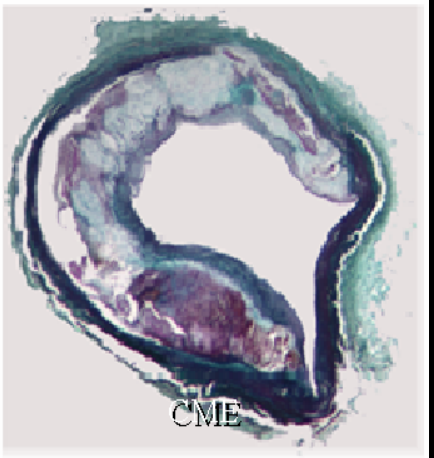
Newer Imaging modalities

QuickTime?and a
TIFF (Uncompressed) decompressor
are needed to see this picture.



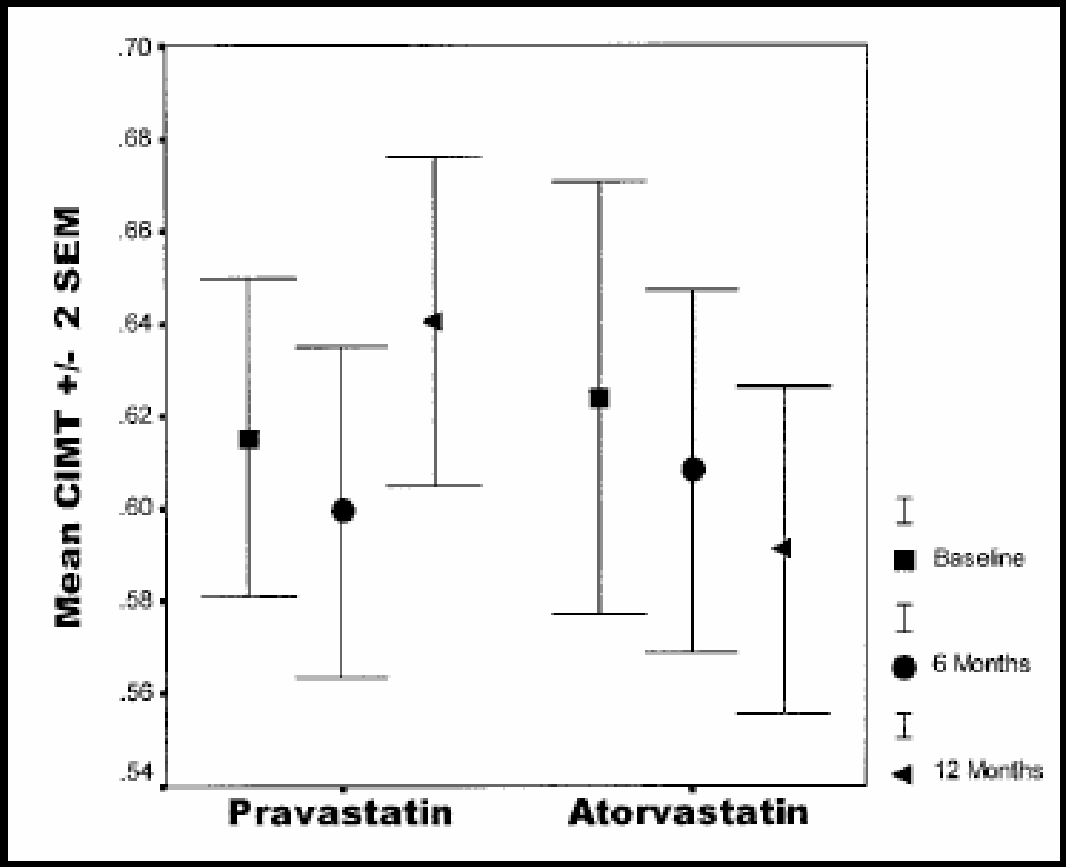






- Pathobiology
- Vessel Wall Imaging
- Effects of Statins

Effects of Statins: carotid IMT



Taylor AJ et al. *Circulation* 2002;106:2055-60

Meteor Study

- Primary hypothesis
  - Rosuvastatin 40 mg will regress carotid IMT
- Objective
  - Reduction in carotid IMT detected by repeated studies over 2 years, in a low risk cohort 10 yr risk <10%.
- Null hypothesis
  - Treatment will progress or not change carotid IMT

Crouse et al. JAMA 2007;297:1344-53.

Reversal Study

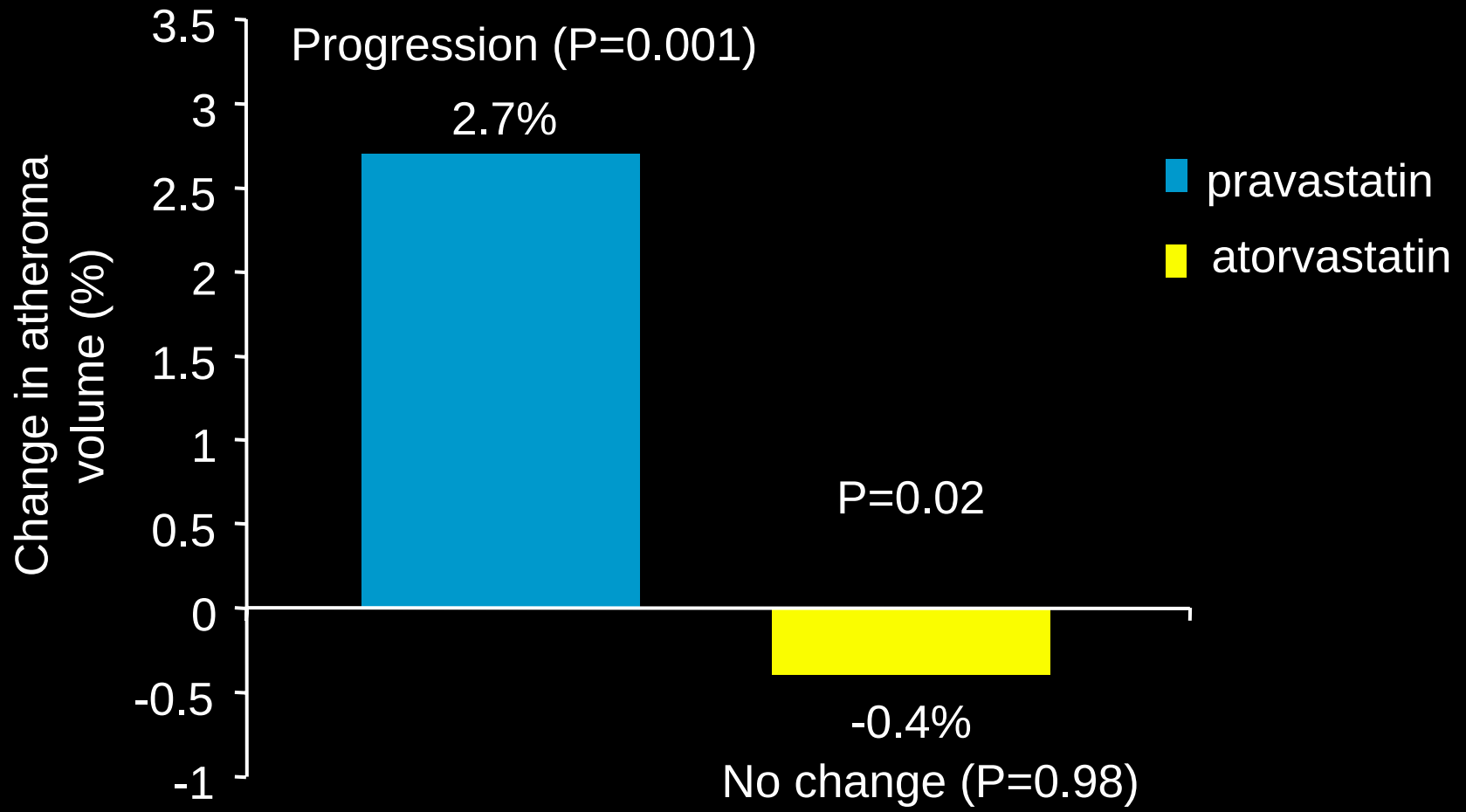
REVERSAL - Final Lipid Values

Lipid Value (mg/dL)	pravastatin 40 mg (n=249)		atorvastatin 80 mg (n=253)		P value*
	Final value	Change (%)	Final value	Change (%)	
Total cholesterol	188±32	-18.4	151±39	-34.1	<0.001
LDL-cholesterol	110±26	-25.2	79±30	-46.3	<0.001
HDL-cholesterol	45±11	+5.6	43±11	+2.9	0.06
Triglycerides	166±92	-6.8	148±95	-20.0	<0.001

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

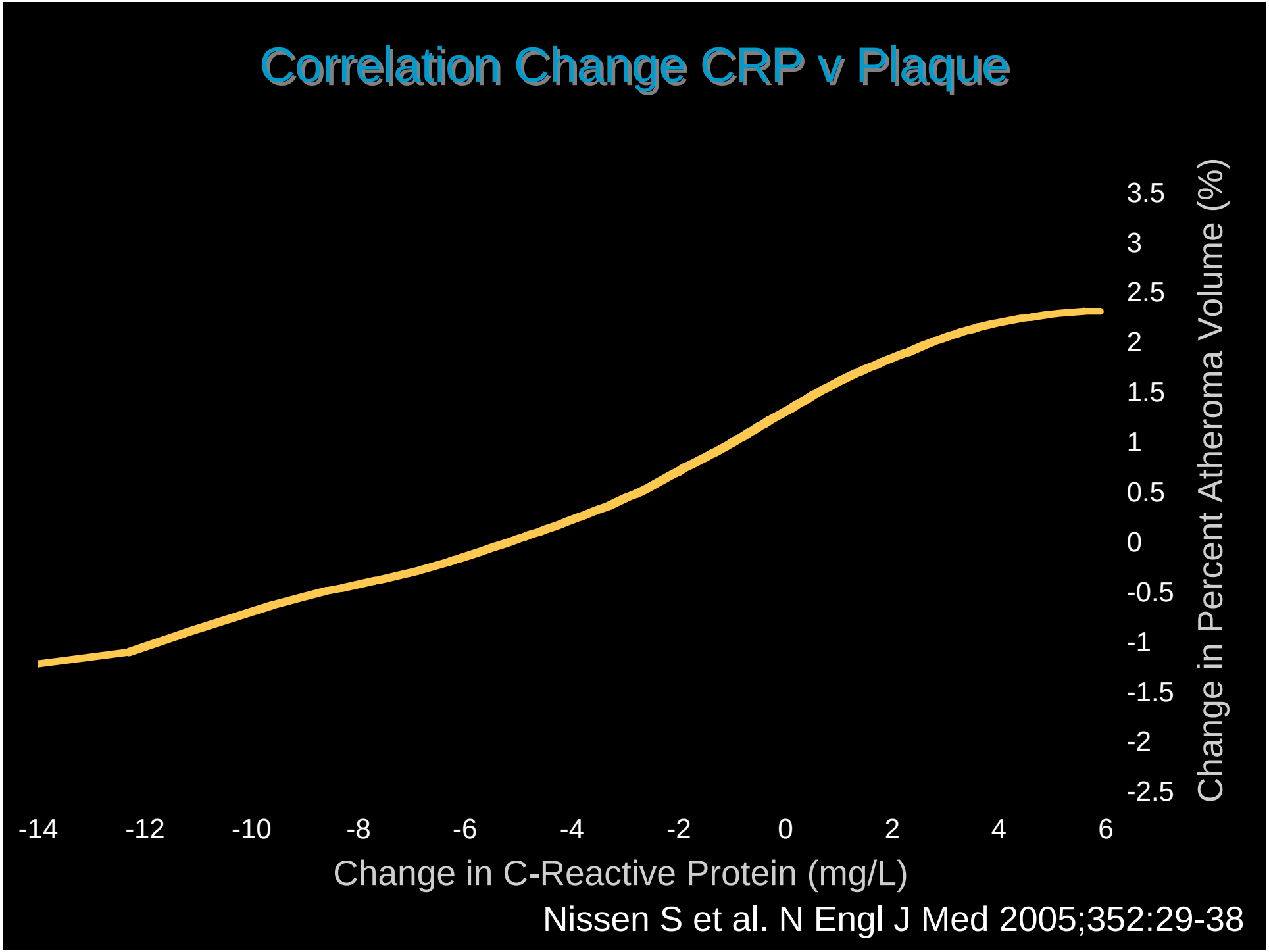
Reversal Study

Percent Change in Atheroma Volume



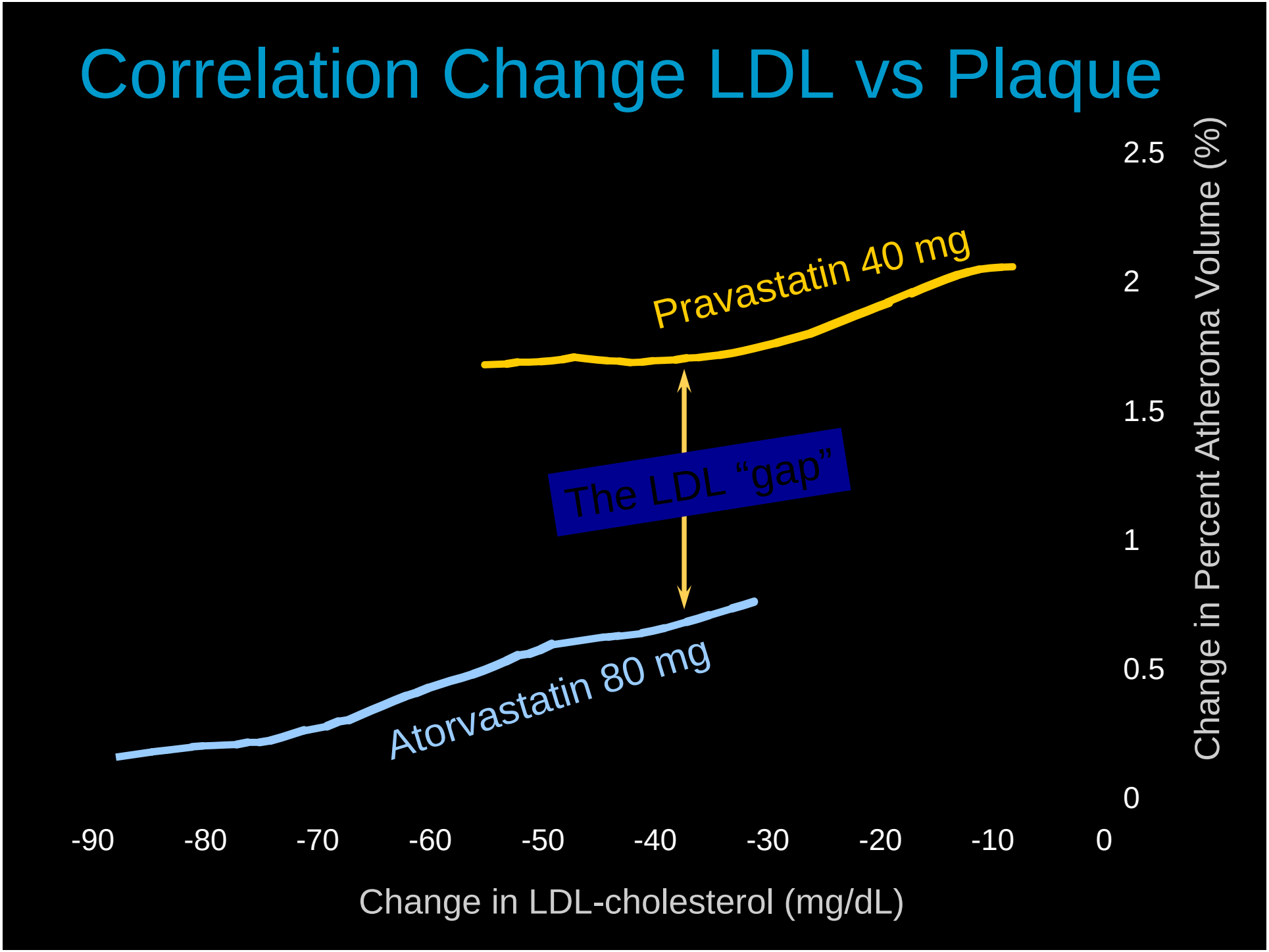
Nissen S et al. *JAMA* 2004;291:1071–80

Correlation Change CRP v Plaque



Nissen S et al. N Engl J Med 2005;352:29-38

Correlation Change LDL vs Plaque



Asteroid Study

- Primary hypothesis
  - 24 months rosuvastatin 40 mg will regress coronary AT
- Objective
  - Reduction in coronary AT detected by separate IVUS studies
- Null hypothesis
  - Treatment will progress or not change coronary AT

Asteroid Study

1183 patients screened and 507 patients treated at 53 centers in US, Canada, Europe and Australia

↓

Intravascular ultrasound with 40 MHz transducer motorised pullback at 0.5mm/sec through >40mm length of single “target” coronary artery

↓

Rosuvastatin 40 mg for 24 months treatment

↓

158 patients withdrew or did not have an evaluable final IVUS

↓

Follow-up IVUS of originally imaged “target” vessel (n=349)

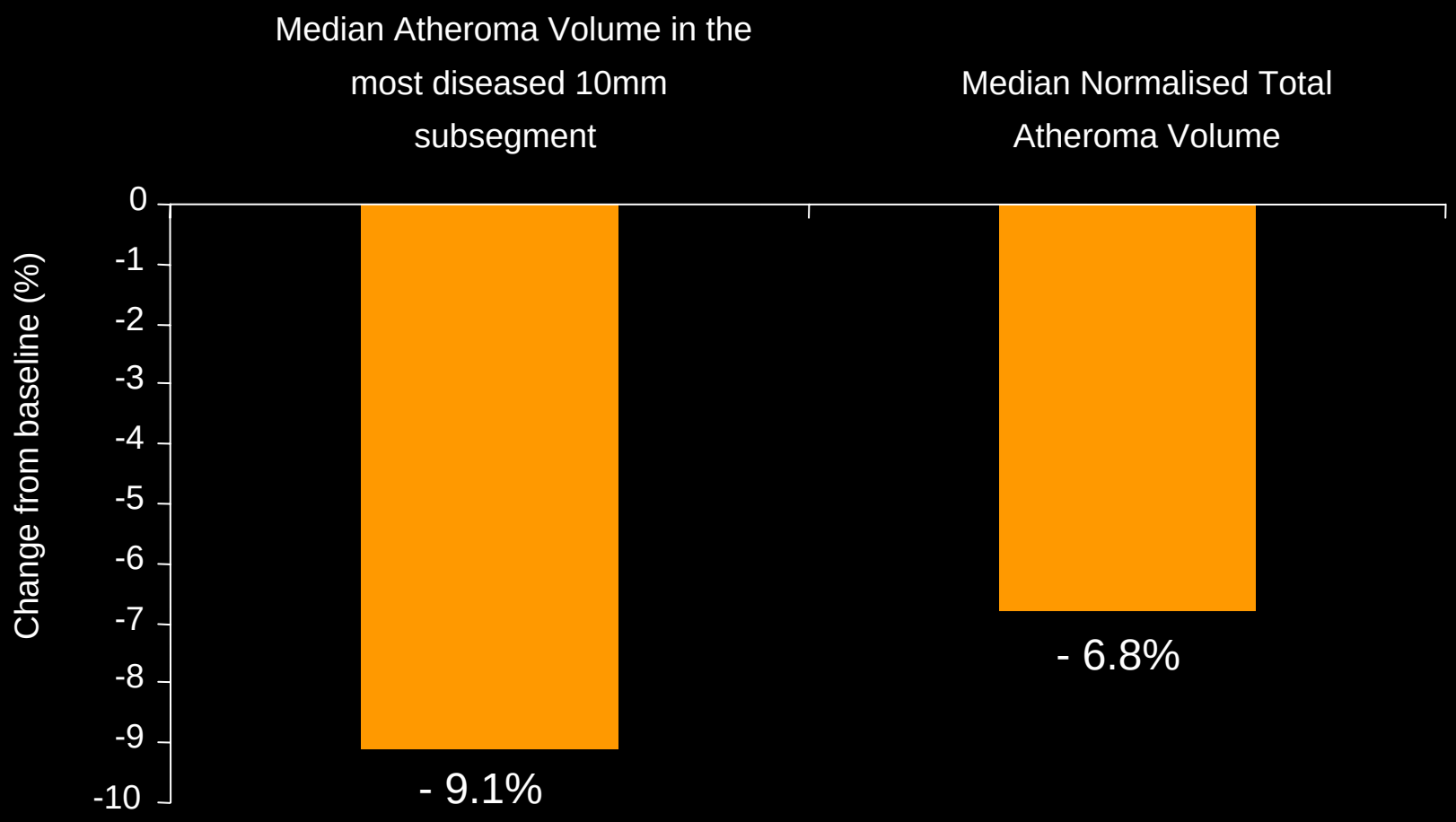
Atherosclerosis and Statins

Lipid Values and Percent Change (n=349)

	Mean Baseline	During treatment*	Percent change†	P value
Total cholesterol (mg/dL)	204	133.8	-33.8	<0.001
LDL-C (mg/dL)	130.4	60.8	-53.2	<0.001
HDL-C (mg/dL)	43.1	49.0	+14.7	<0.001
Triglycerides (mg/dL)	152.2	121.2	-14.5	<0.001
LDL-C/HDL-C ratio	3.2	1.3	-58.5	<0.001

Nissen SE et al. *JAMA* 2006;295:1556-65.

ASTEROID - Serial IVUS Data

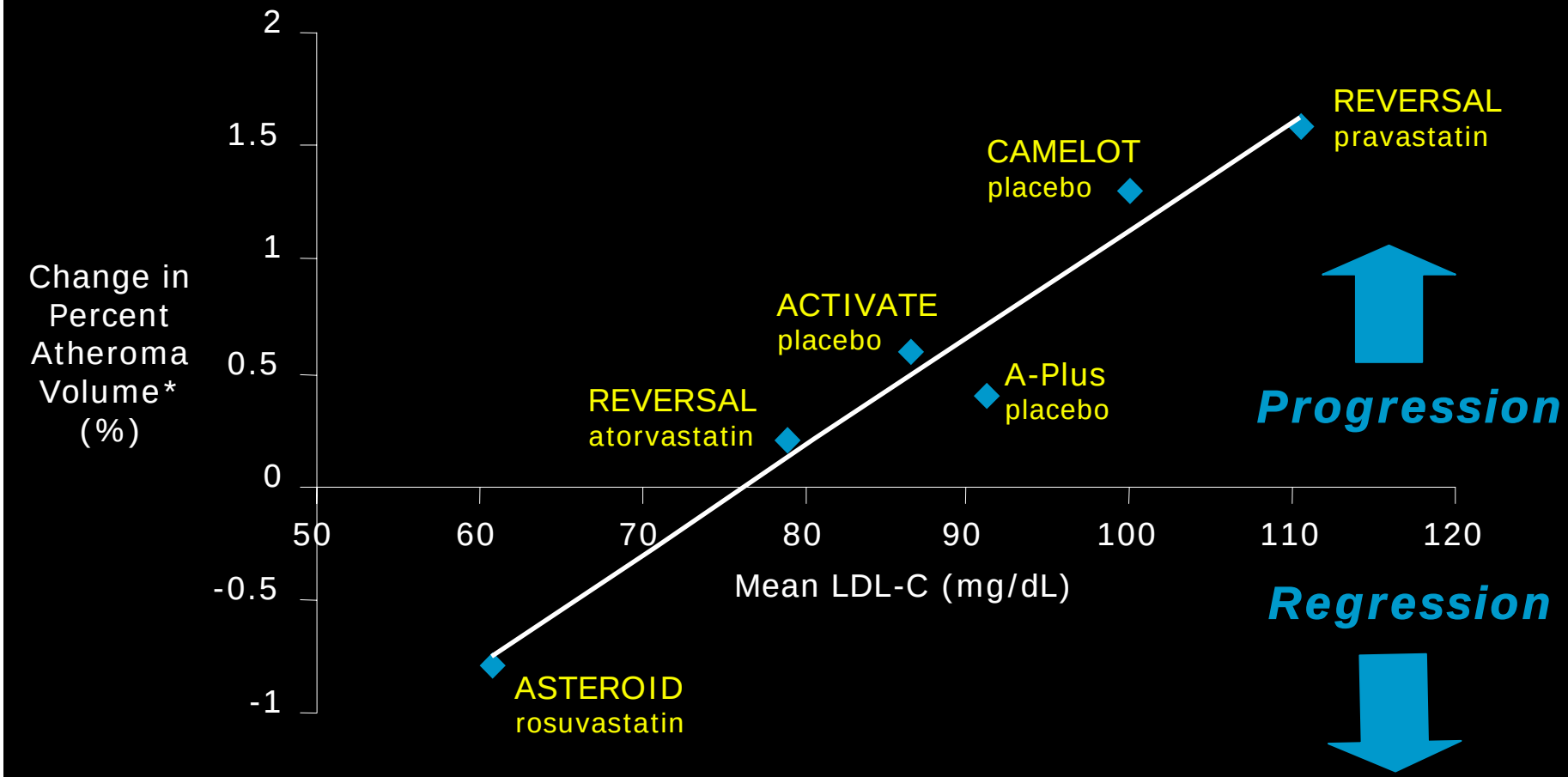


Rosuvastatin is not indicated for atherosclerosis regression

Nissen SE et al. *JAMA* 2006;295:1556-65.

Atherosclerosis and Statins

Mean LDL-C and change in % atheroma volume



Rosuvastatin is not indicated for atherosclerosis regression

Atherosclerosis and Statins

Predictors of Atheroma Regression

- 1,455 patients / 4 trials
- Multivariate correlates of Regression
  - LDL chol reduction (<87.5mg/dL)
  - HDL chol increase (>7.5%)

Nicholls SJ et al. *JAMA* 2007;297:499-508.

Relationship Between LDL-c and HDL-c with Atheroma Progression or Regression

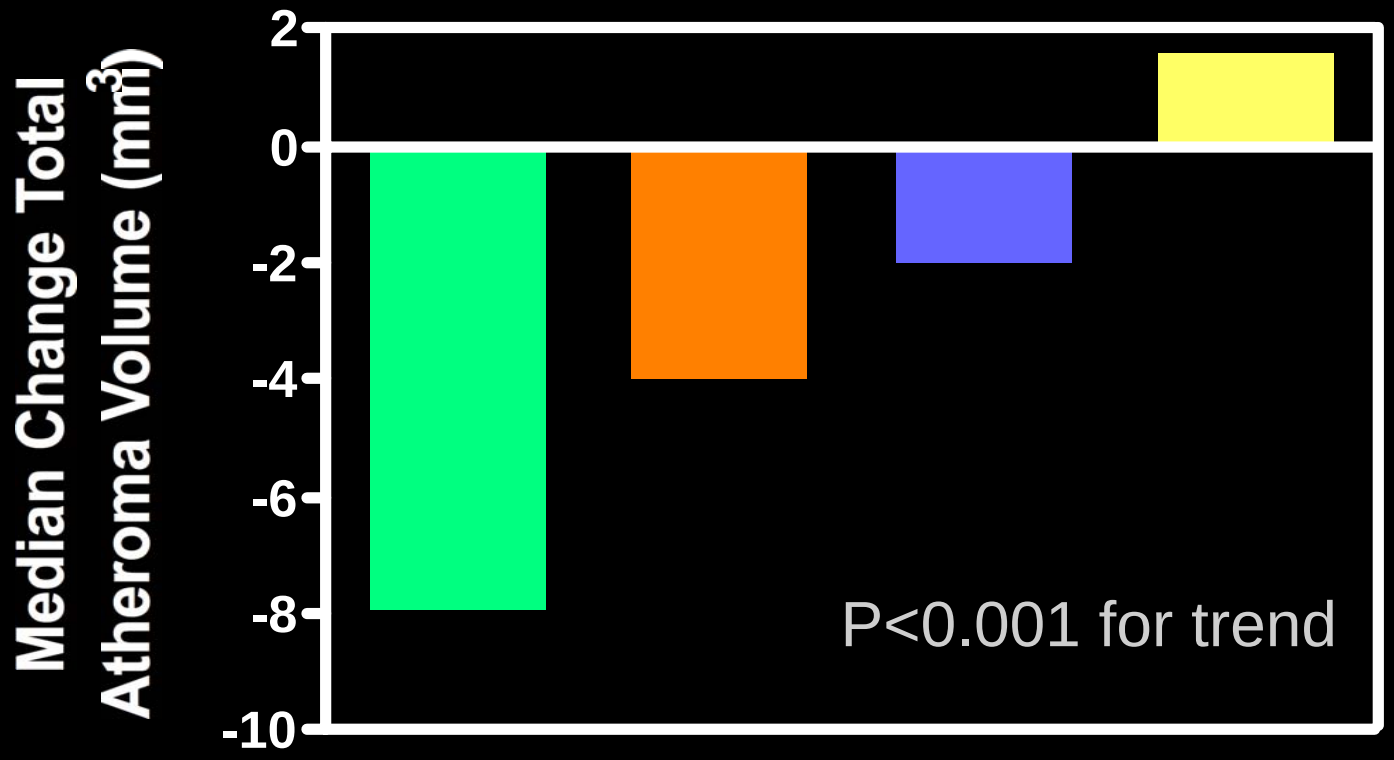
Table 6. Relationship Between the Combination of Level of Low-Density Lipoprotein Cholesterol During Treatment and Change in High-Density Lipoprotein Cholesterol With Atheroma Progression or Regression

	LDL-C Level During Treatment, mg/dL	% Change in HDL-C Level	Change in PAV, Mean (SD) [Median], %	Change in TAV, Mean (SD) [Median], mm^3	MI, %	Stroke, %	Revascularization, %
No. of participants							
276	<87.5	>7.5	−0.4 (3.4) [−0.5]	−8.8 (21.5) [−7.9]	2.1	0.6	32.5
329	<87.5	<7.5	0.2 (3.8) [0]	−2.8 (22.7) [−4.0]	1.2	0	28.1
226	>87.5	>7.5	0.9 (3.9) [0.3]	0.3 (23.0) [−2.0]	0.7	0.3	21.4
309	>87.5	<7.5	1.3 (4.2) [1.1]	2.1 (25.2) [1.6]	2.1	0	28.1
P value*			<.001	<.001	.36	.13	.07

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PAV, percent atheroma volume; TAV, total atheroma volume.
SI conversion factor: To convert low-density cholesterol to mmol/L, multiply by 0.0259.
*Comparison between all groups using analysis of covariance after controlling for any differences in baseline atheroma volume between groups.

Nicholls SJ et al. *JAMA* 2007;297:499-508.

Benefit of Combination HDL Raising and LDL Lowering with Statins



LDL-C	<87.5	<87.5	>87.5	>87.5
Δ HDL-C	>7.5%	<7.5%	>7.5%	<7.5%

Nicholls SJ et al. *JAMA* 2007;297:499-508.

“Man lives with arteriosclerosis,

and dies of the complicating thrombosis”

Dedichen J, Brit Med J 1956;3:1038-9