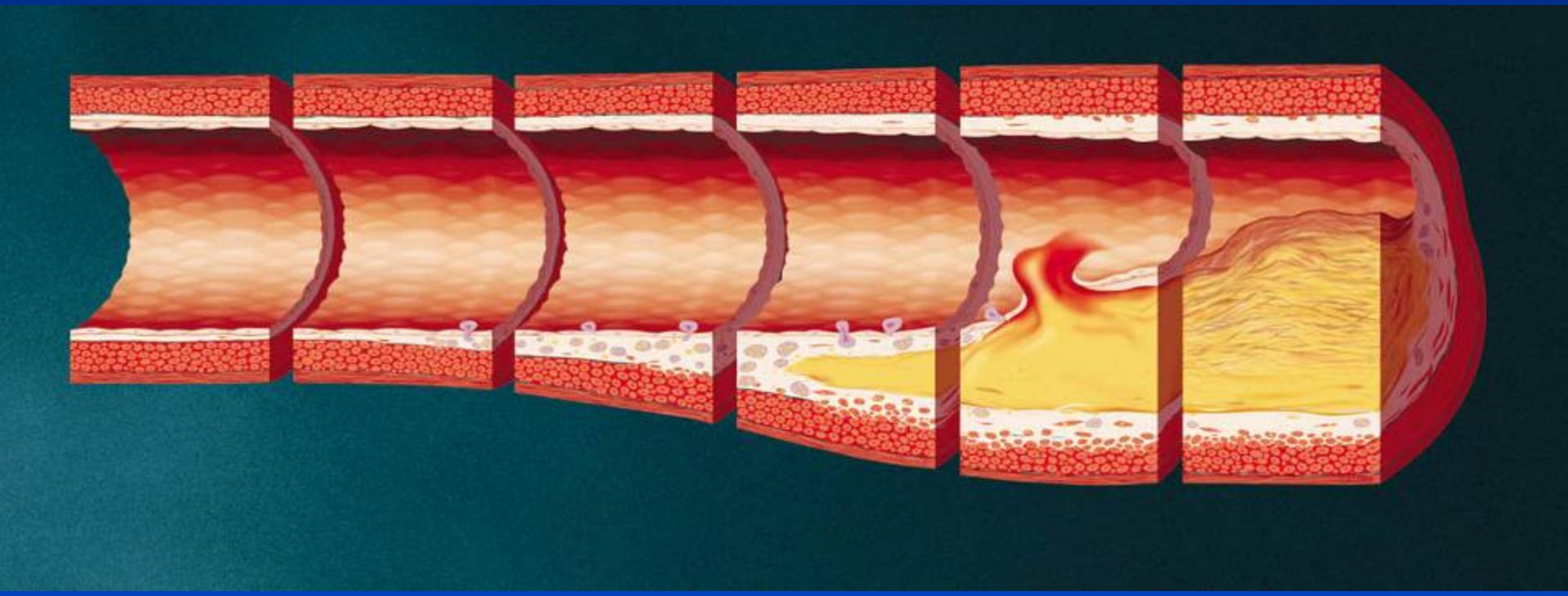
Update of CVD

by
Dr. Deng XiWei

Nov 15, 2008

Vascular remodelling



INTIMA – MEDIA THICKENING

PLAQUE DEVELOPMENT

2008 update

Adapted from Libby P. *Circulation* 2001;104:365-372

Vascular Improvement with Olmesartan Study (VIOS)

Study Design and Primary End-Point

Stage I nondiabetic hypertensive patients (61% male; age 38-67 years) randomized after a 4-week washout period to olmesartan medoxomil 20–40 mg or atenolol 50–100 mg plus additional agents (hydrochlorothiazide, amlodipine or hydralazine) **as needed for a goal BP ≤120/80 mm Hg**

At baseline and after 1 year of treatment, subcutaneous gluteal resistance arteries were examined on a pressurized myograph to evaluate remodeling.

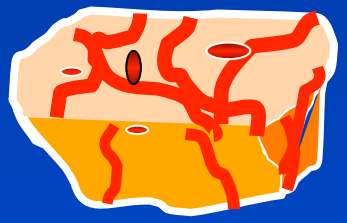
- **The primary endpoint was the degree of vascular remodeling as obtained from changes in wall-to-lumen ratio of gluteal subcutaneous resistance vessels obtained from percutaneous biopsy of patients assigned to each of two treatment arms compared to the normal volunteers**

Smith et al. Journal of the Am Soc. of Hypertension, 2008; 2 (3), 165-172

Methodology for Study of Human Resistance Arteries

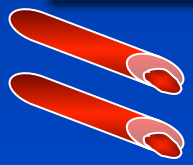
Gluteal subcutaneous biopsy

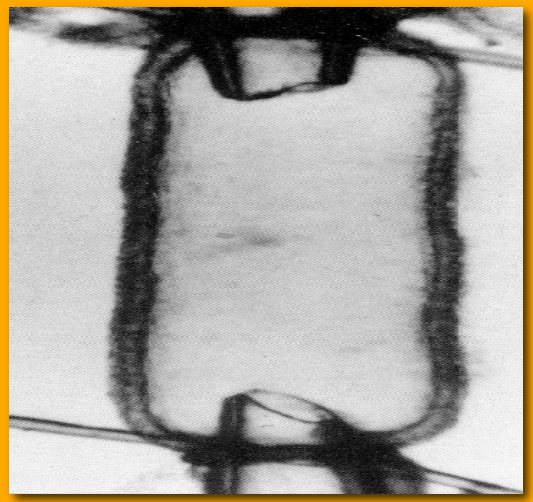
Subcutaneous fat



Peripheral resistance artery (150 ~350 µm)

Dissection

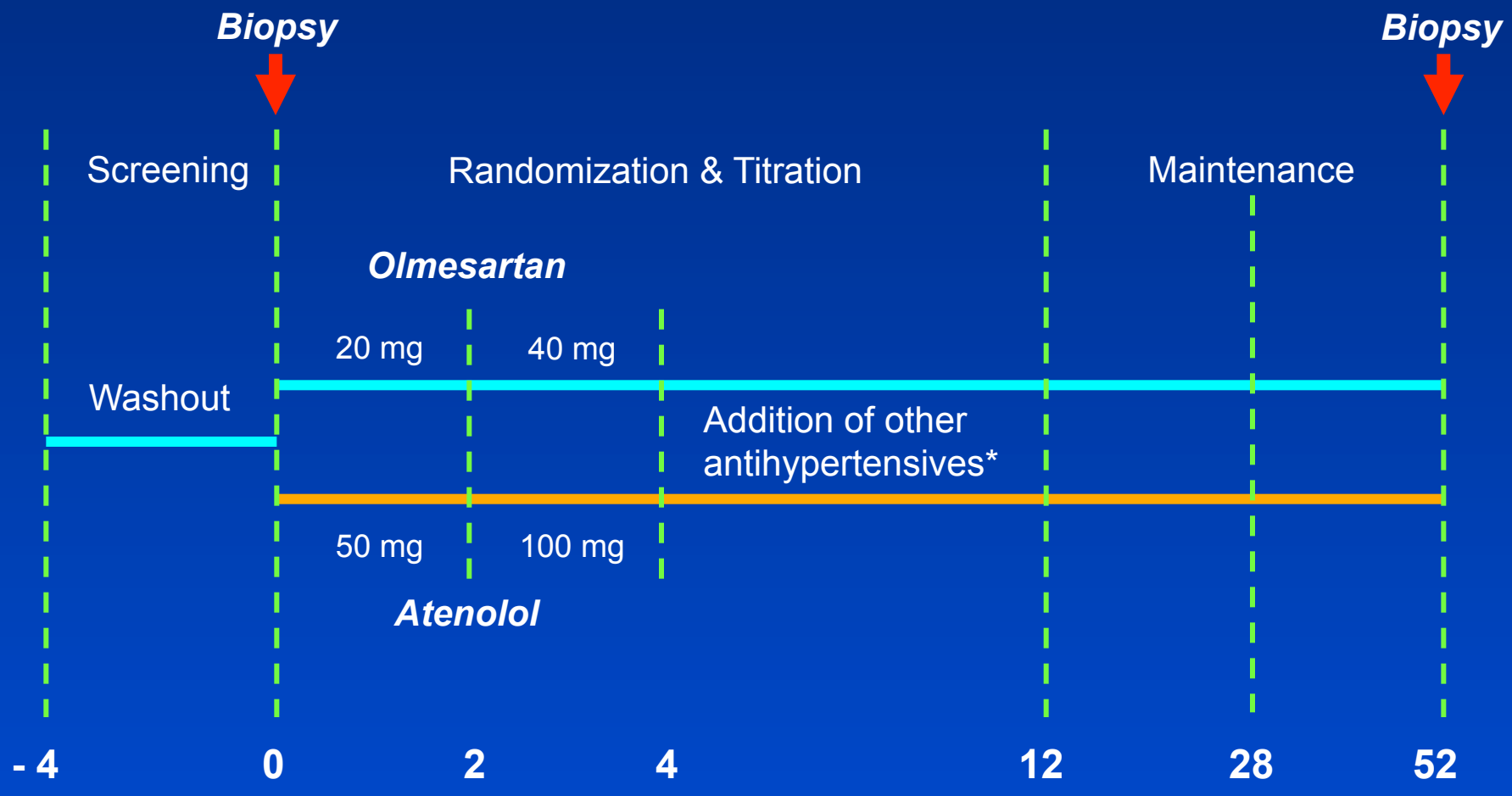




Isobaric

Modified from E Schiffrin, MD, PhD

VIOS
Study design

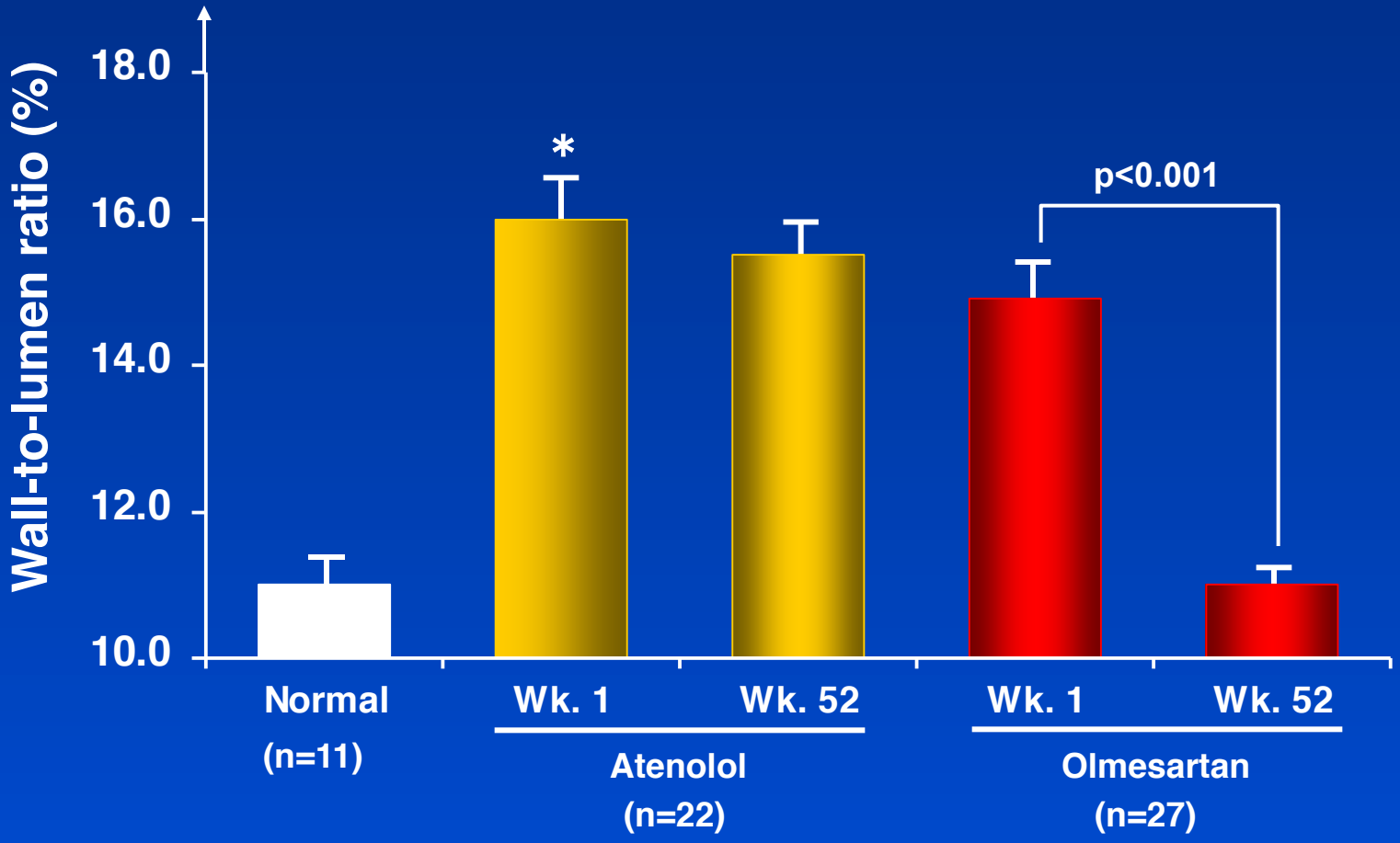


N=100
* Hydrochlorothiazide, amlodipine, hydralazine

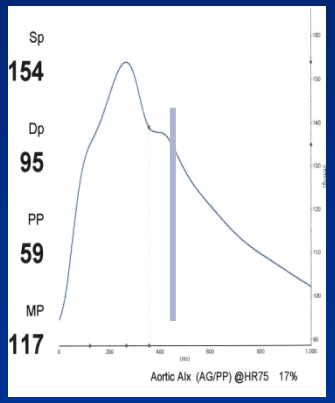
2008 update

Smith RD, et al. *Am J Cardiovasc Drugs* 2006;6:335-342

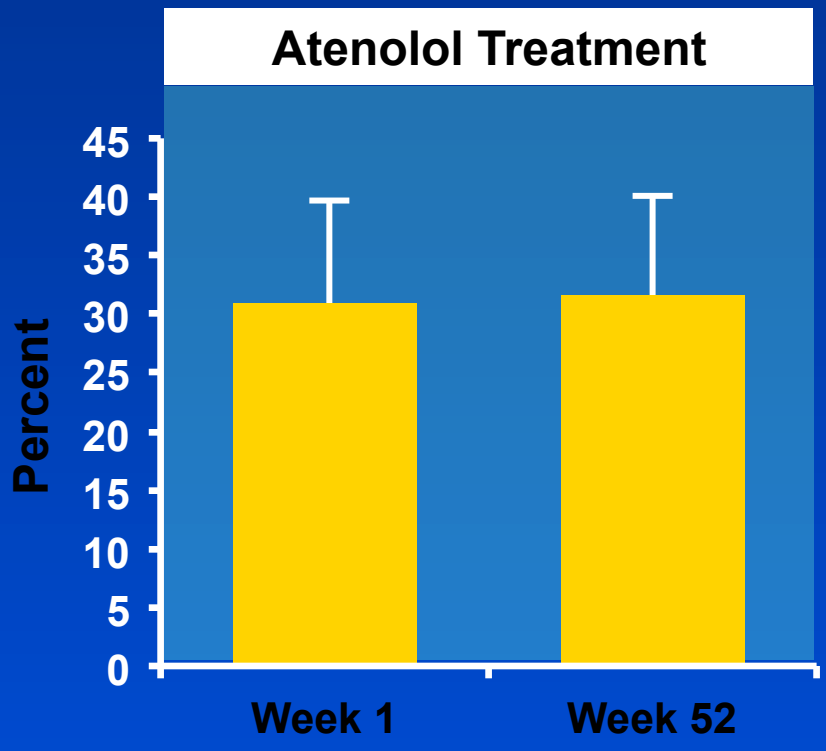
Results:
Change in wall-to-lumen ratio

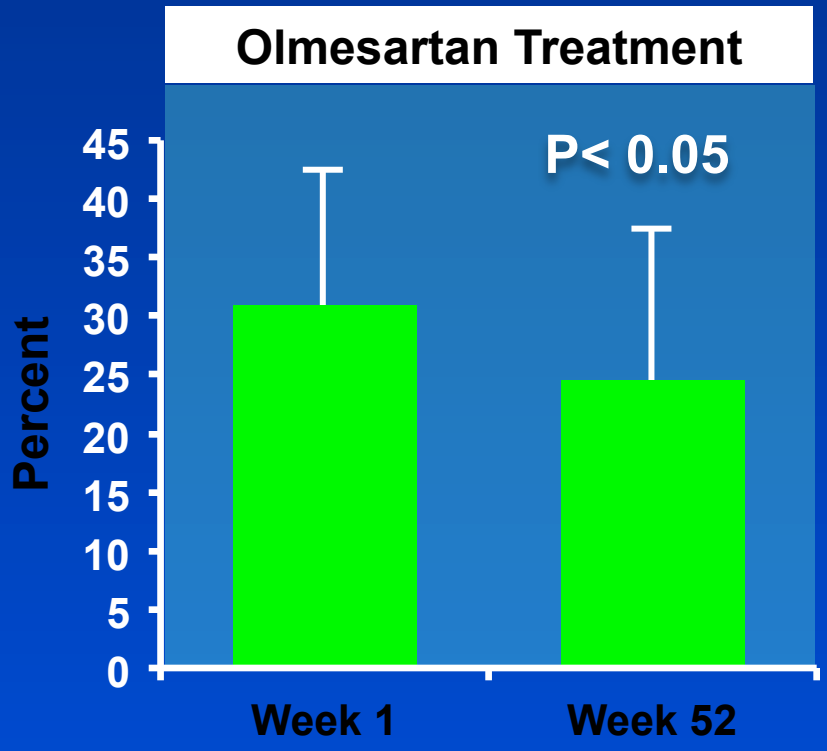


Yokoyama H, et al. *Am J Hypertens* 2005;18(5, Part 2):23A (abstract P-42)



Effect of Treatments on Augmentation Index (AG/PP)





Values are Means ± SD

Smith et al. *J of Am Soc Hypert 2008, in press*

Vascular remodelling may be independent of blood pressure effects

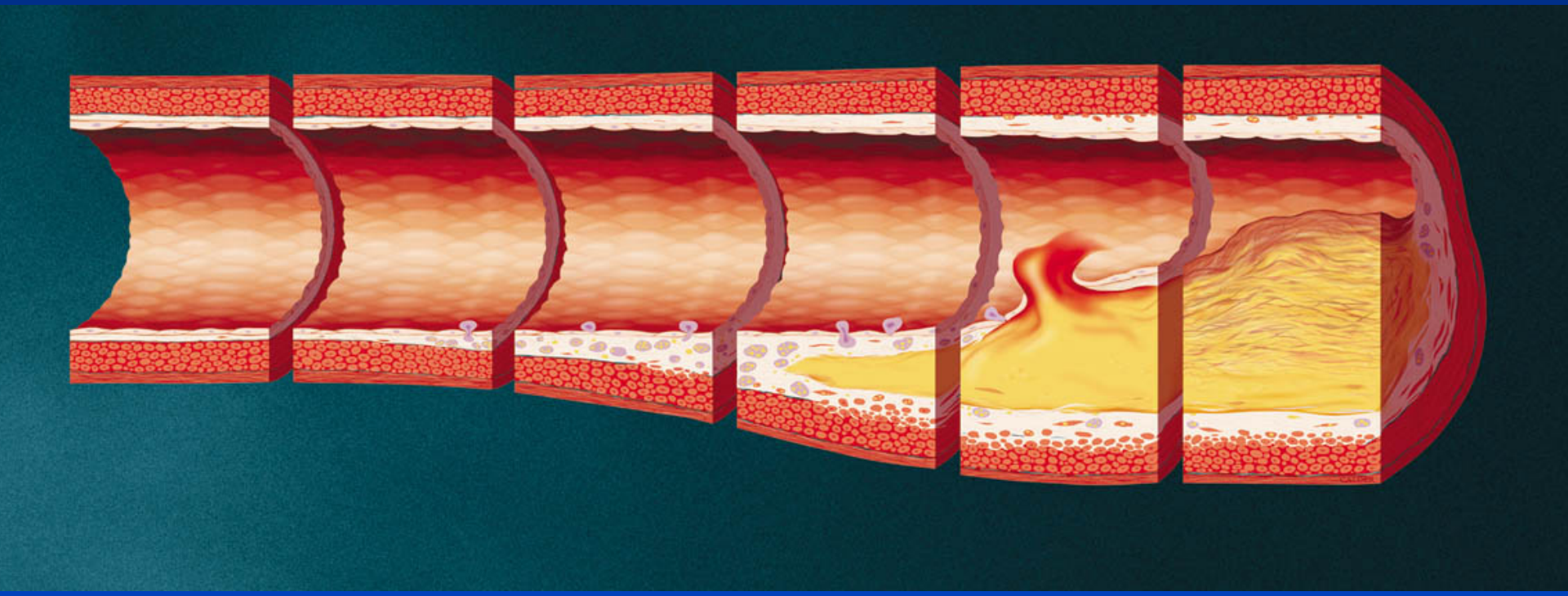
- The two treatment groups achieved a comparable level of blood pressure control
  - Mean blood pressure for study group: 122/77 ± 11/6 mmHg
- Thus, the effect of olmesartan on vascular remodelling is likely to be independent of its blood pressure-lowering effects

- In the presence of nearly physiological blood pressure control, suppression of the renin-angiotensin system by blockade of the AT_1 receptor with olmesartan reverses small resistance vessel remodeling to virtually normal, while adrenergic system suppression with atenolol has little to no effect

Yokoyama H, et al. *Am J Hypertens* 2005;18(5, Part 2):23A (abstract P-42)

2008 update

Vascular structure is adversely altered due to intima-media thickening and plaque development

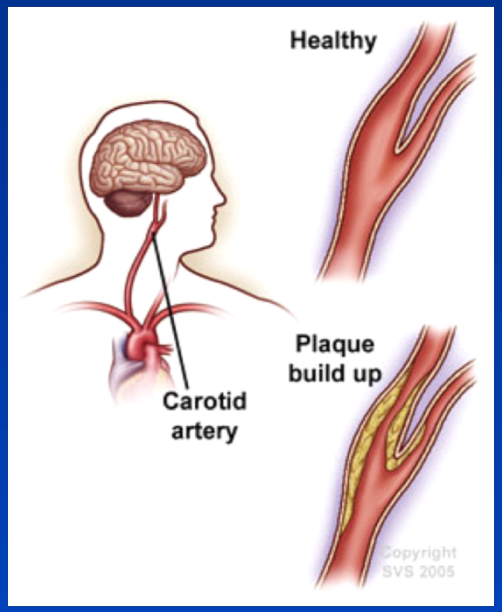


INTIMA – MEDIA THICKENING

PLAQUE DEVELOPMENT

Adapted from Libby. Circulation 2001;104:365–72

The Cardiovascular Continuum

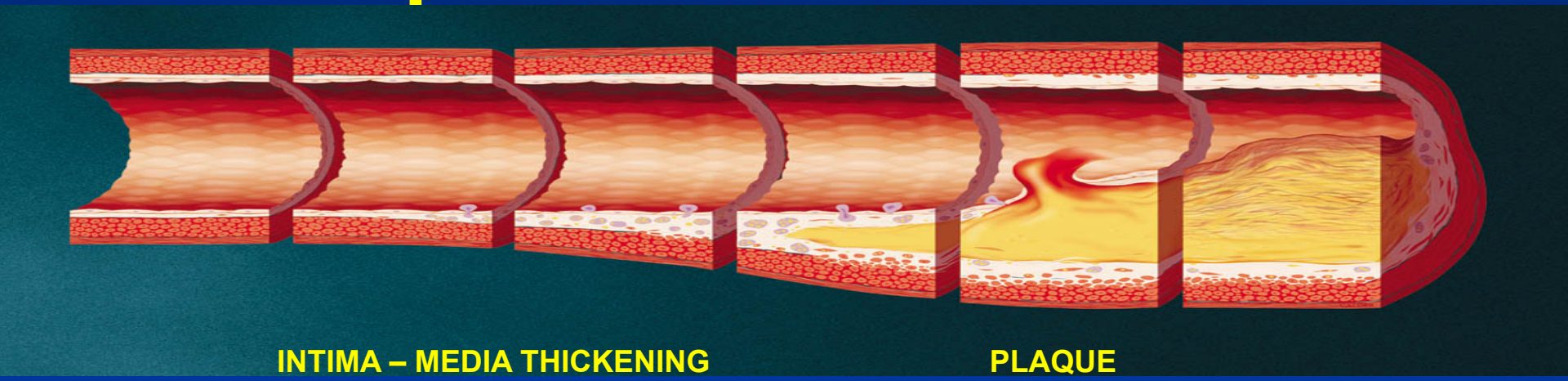


- OBJECTIVE -

The MORE is testing the hypothesis that for the same level of blood pressure control, OLMESARTAN is superior to Atenolol in reversing or slowing progression of atherosclerotic plaques in the common carotid artery or the carotid bulb in hypertensive subjects with high risk for cardiovascular events

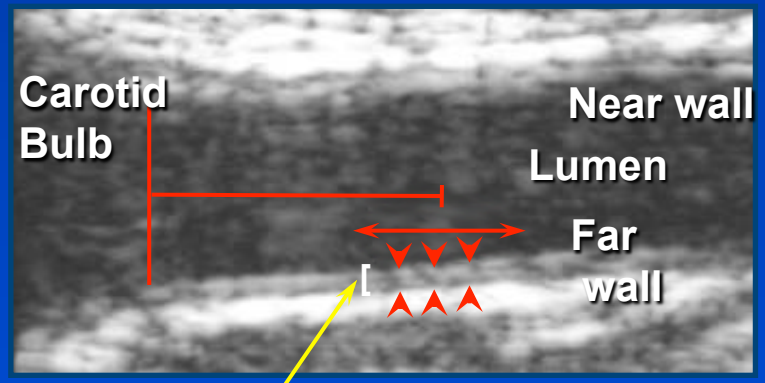
Stumpe KO. Clin Ther 2004;26:A33-A37
Stumpe et al. Therap. Advances in Cardiovas. Disease 2007;1:97-106

Development of Atherosclerosis



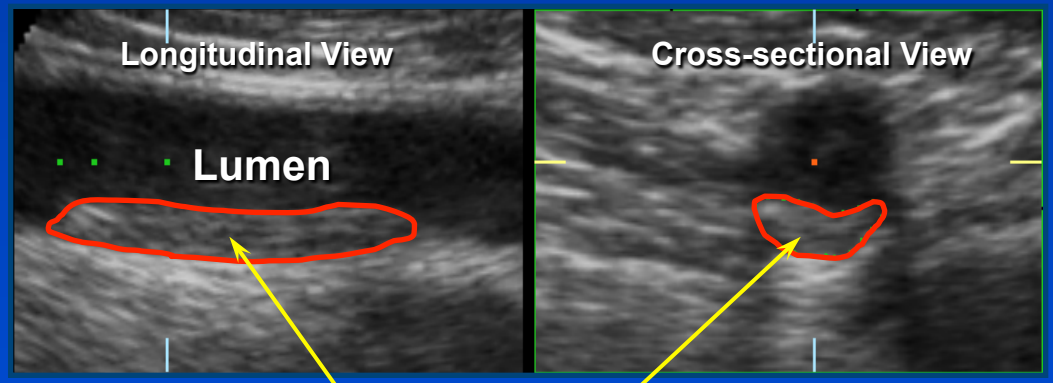
THE MORE STUDY: Ultrasound Measurements

2-D Ultrasound
Carotid IMT



IMT = 1.1 mm

3-D Ultrasound
Carotid Plaque



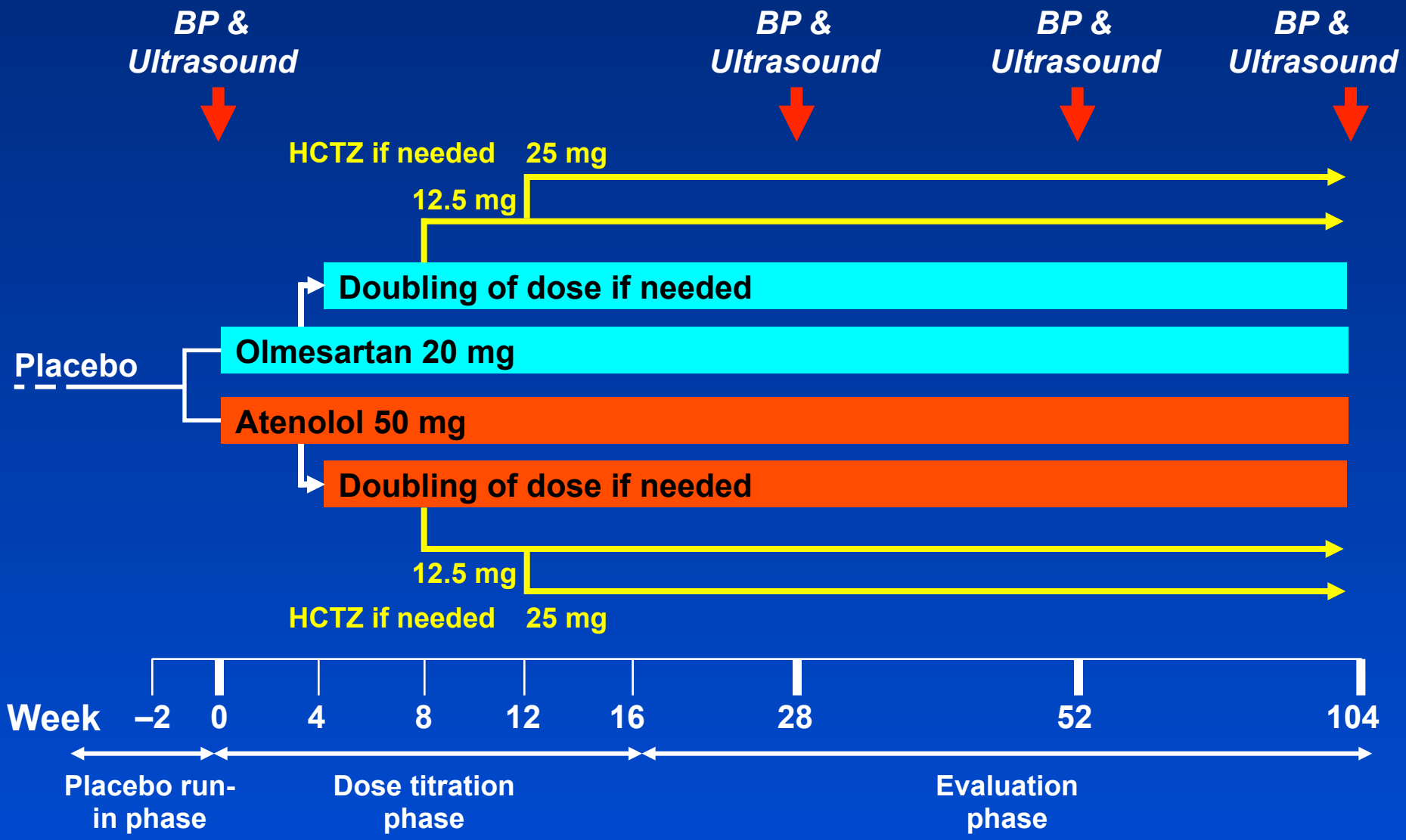
Plaque Volume = 202 µl

Design and end-points in the MORE study

- **Multicentre, double-blind, randomised study**
- **Patients received 104 weeks of therapy with olmesartan medoxomil or atenolol**
  - Elective titration: olmesartan (20–40 mg od) vs atenolol (50–100 mg od), addition of HCTZ (12.5–25 mg) if required for BP control
- **The primary end-point was the change in IMT in the common carotid artery from baseline after 104 weeks' treatment**
- **Secondary end-points assessed included:**
  - Change in common carotid PV and overall IMT from baseline after 28, 52 and 104 weeks' treatment
  - Change in SBP and DBP from baseline after 28, 52 and 104 weeks

Stumpe et al. Ther Adv Cardiovasc Dis 2007;1(2):97–106

Design of the MORE study

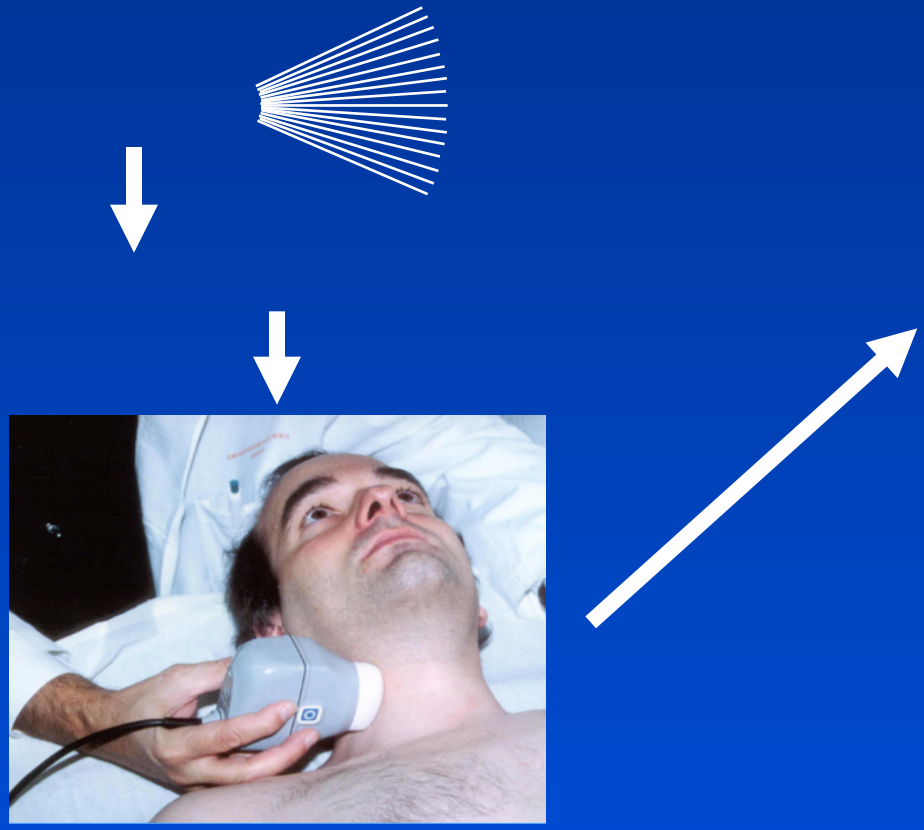


HCTZ = hydrochlorothiazide

Stumpe et al. Ther Adv Cardiovasc Dis 2007;1(2):97–106

The non-invasive 3D ultrasound technique used in the MORE study

Mechanical driven
3D probe (10 MHz, 0.1 mm resolution)



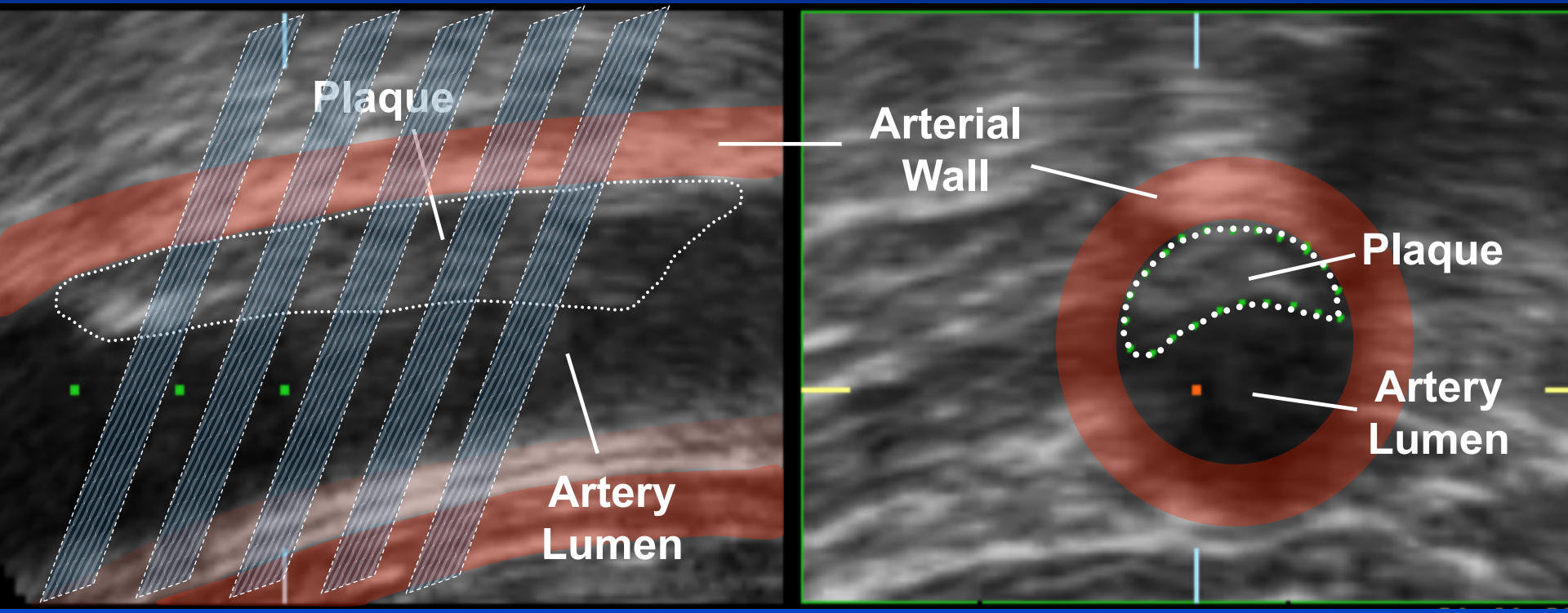
Voluson 530 ultrasound system
(Kretz-Technik AG, Zipf, Austria)

Daiichi-Sankyo data on file 2007

The PV measurements in MORE are built up from longitudinal and cross-sectional ultrasound (US) scans

View of a longitudinal US scan

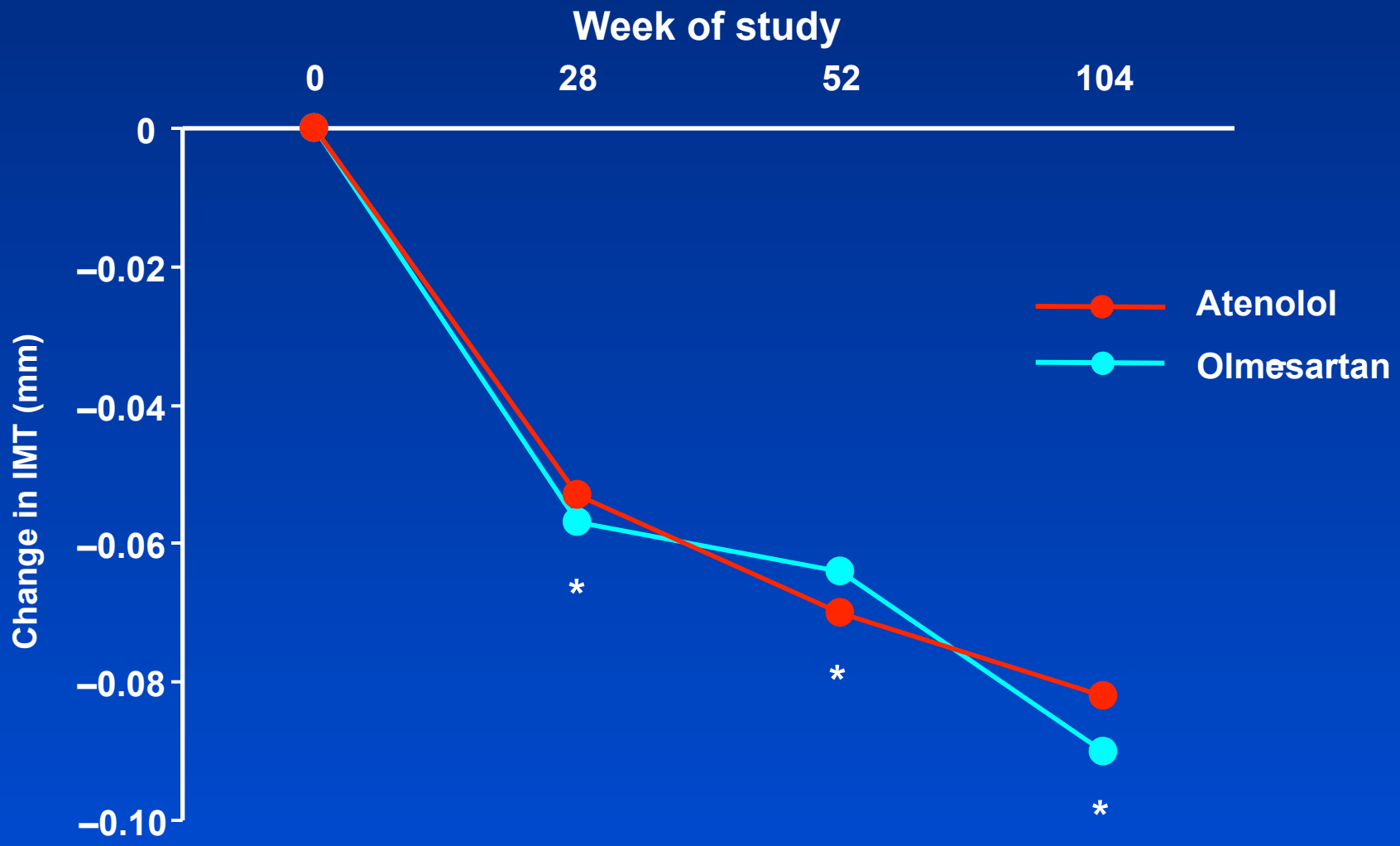
View of a cross-sectional US scan



A longitudinal US scan of a plaque is combined with a series of cross-sectional scans to produce a 3D measurement of PV

Daiichi-Sankyo data on file 2007

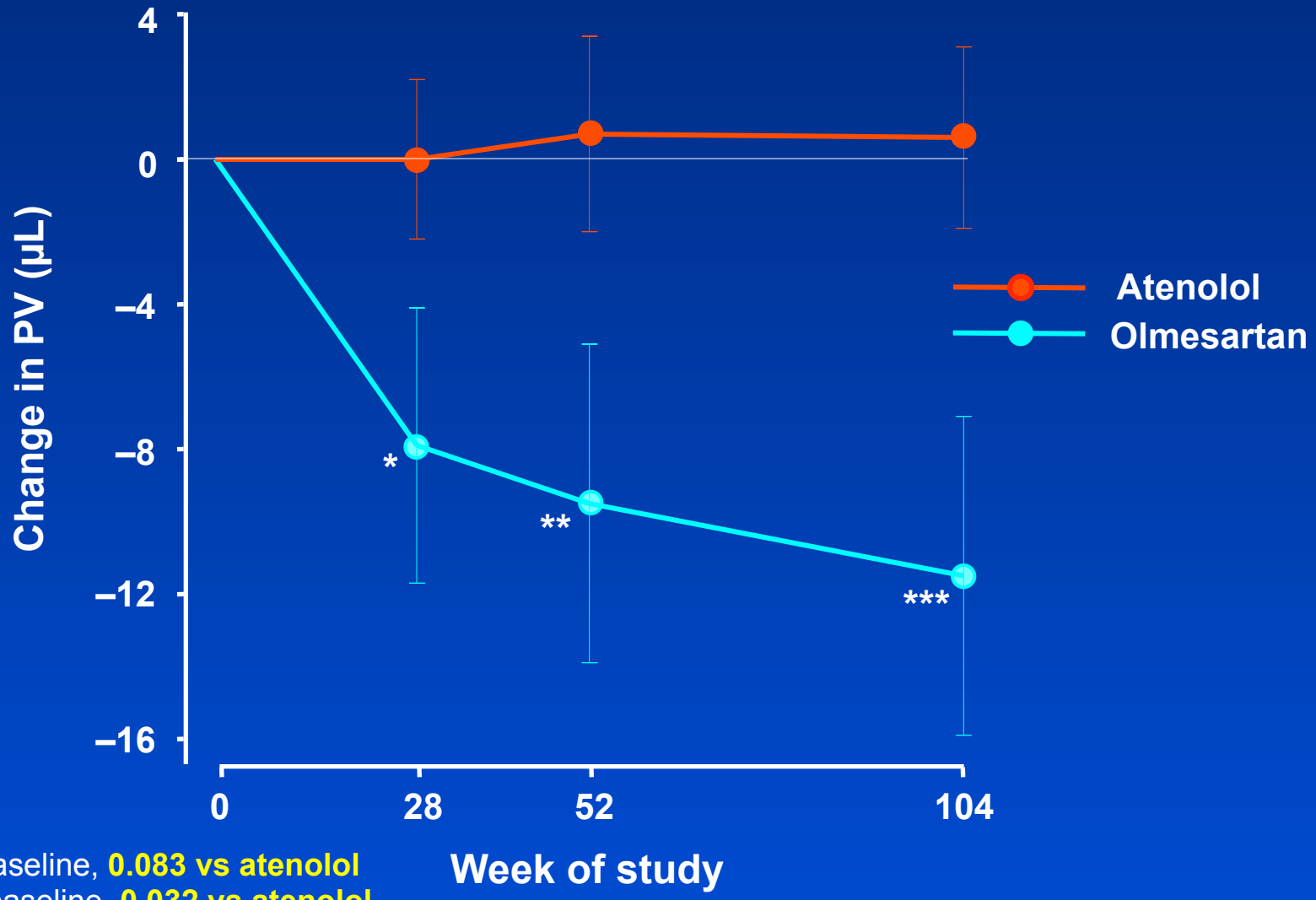
Change in IMT over time during the MORE study (ITT population)



*p<0.0001 vs baseline for each treatment

Stumpe et al. Ther Adv Cardiovasc Dis 2007;1(2):97–106

Change over time in PV in patients whose PV was ≥ baseline median (ITT population)



*p=0.044 vs baseline, **0.083 vs atenolol**
p=0.036 vs baseline, **0.032 vs atenolol
***p=0.014 vs baseline, **0.023 vs atenolol**

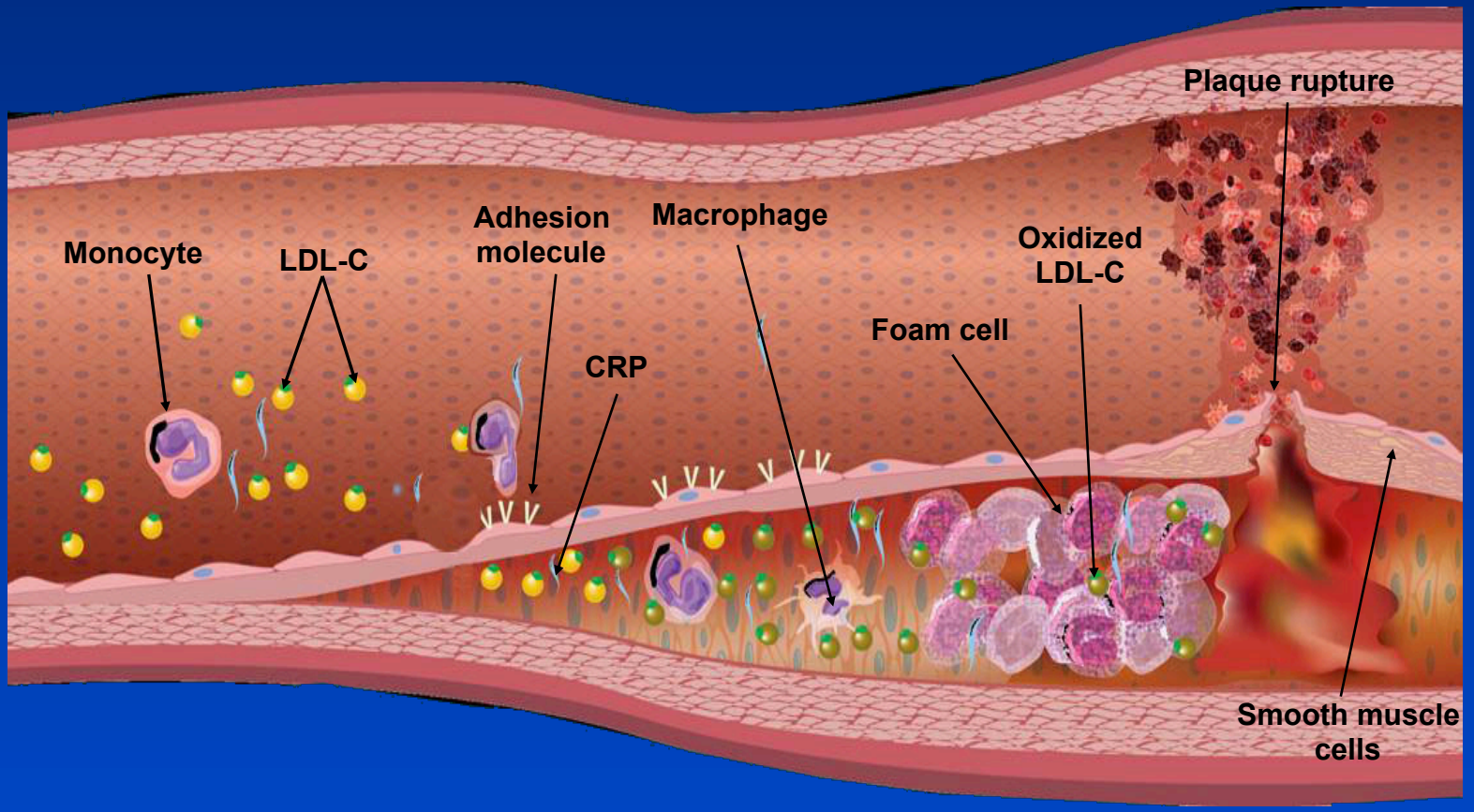
Stumpe et al. Ther Adv Cardiovasc Dis 2007;1(2):97–106

Conclusions

- **The MORE study is the first to show PV regression following treatment with an ARB**
- **In the MORE study, 2 years' treatment with olmesartan and atenolol produced similar significant reductions in IMT**
  - Given the association between increased IMT and cardiovascular risk, such reductions should have a beneficial effect on patients' level of cardiovascular risk
- **In contrast to atenolol, olmesartan significantly reduced the volume of larger atherosclerotic plaques**
- **The treatment difference between olmesartan and atenolol in the volume of larger plaques was evident at 28 weeks and progressively increased throughout the study**
- **Comparable reductions in BP with olmesartan and atenolol were observed, suggesting that the anti-atherosclerotic activity of olmesartan is independent of its BP-lowering effects**

Vasculoprotective Effects of Atorvastatin

Atherosclerosis: A Progressive Disease



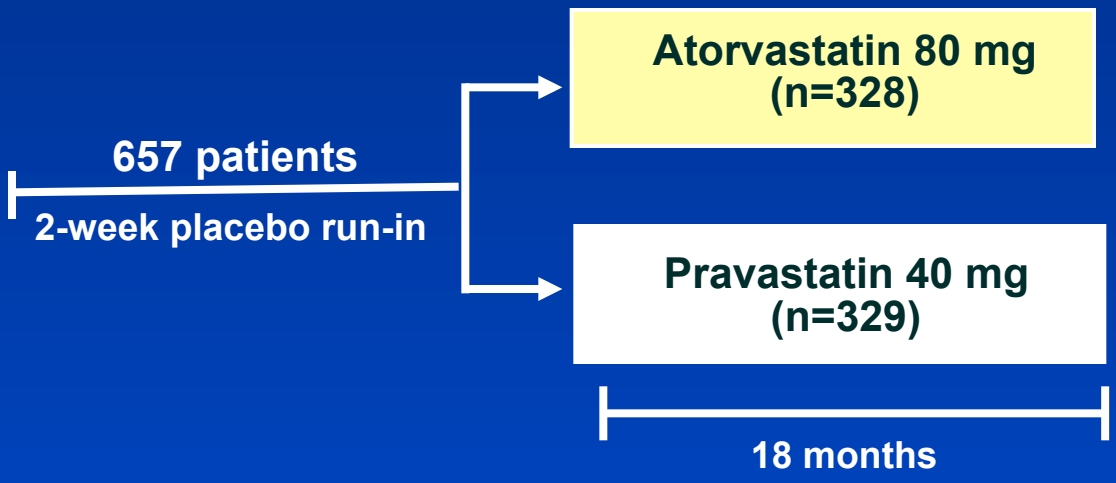
CRP=C-reactive protein; LDL-C=low-density lipoprotein cholesterol.

Libby P. *Circulation.* 2001;104:365-372; Ross R. *N Engl J Med.* 1999;340:115-126.

Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL): Study Design

Patient population

- Men and women aged 30-75 years requiring coronary angiography
- ≥1 obstruction, with luminal diameter narrowing of ≥20%
- LDL-C 125-210 mg/dL following 4- to 10-week washout

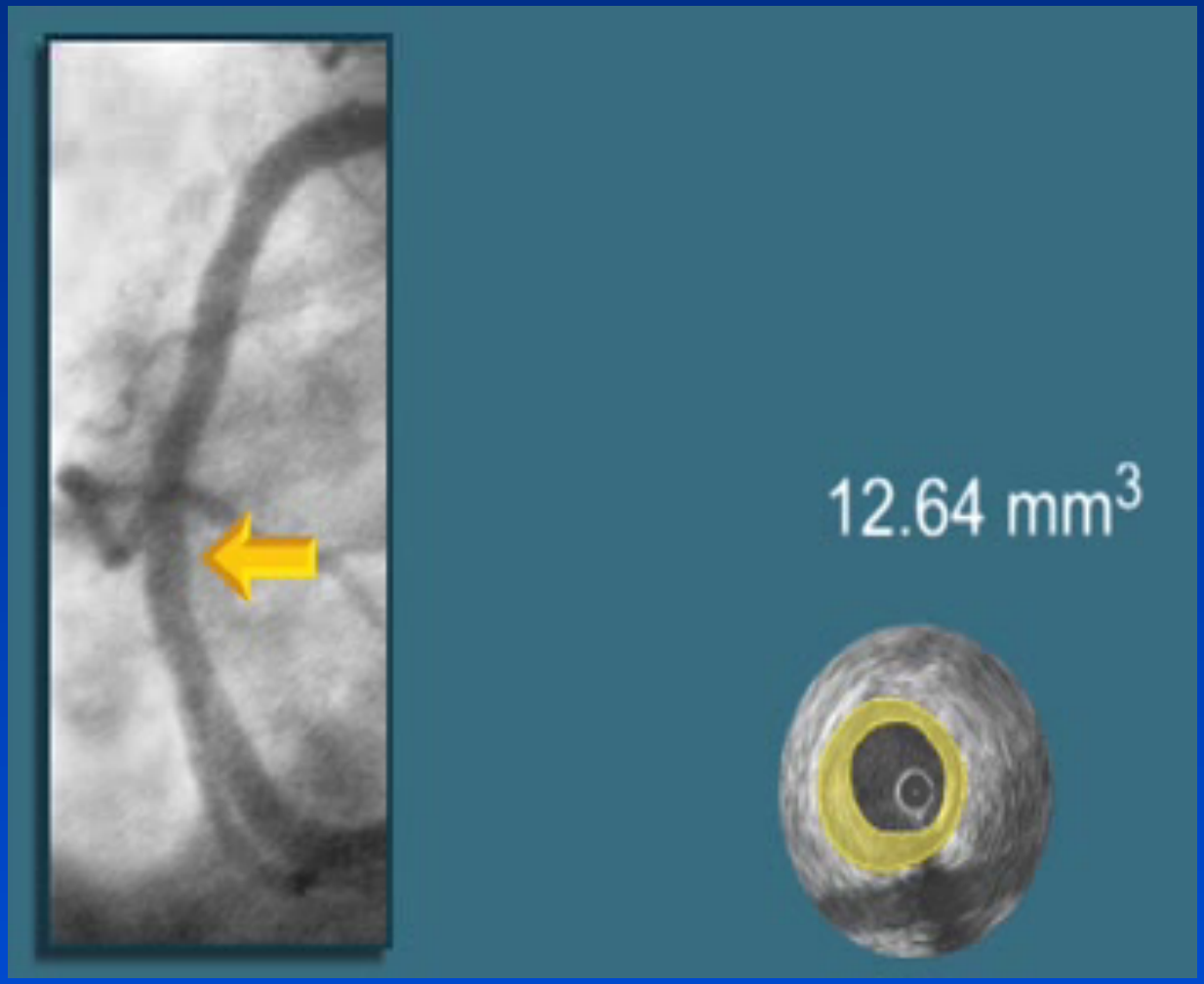


Primary efficacy end point

- Percentage change in atheroma volume (follow-up minus baseline)

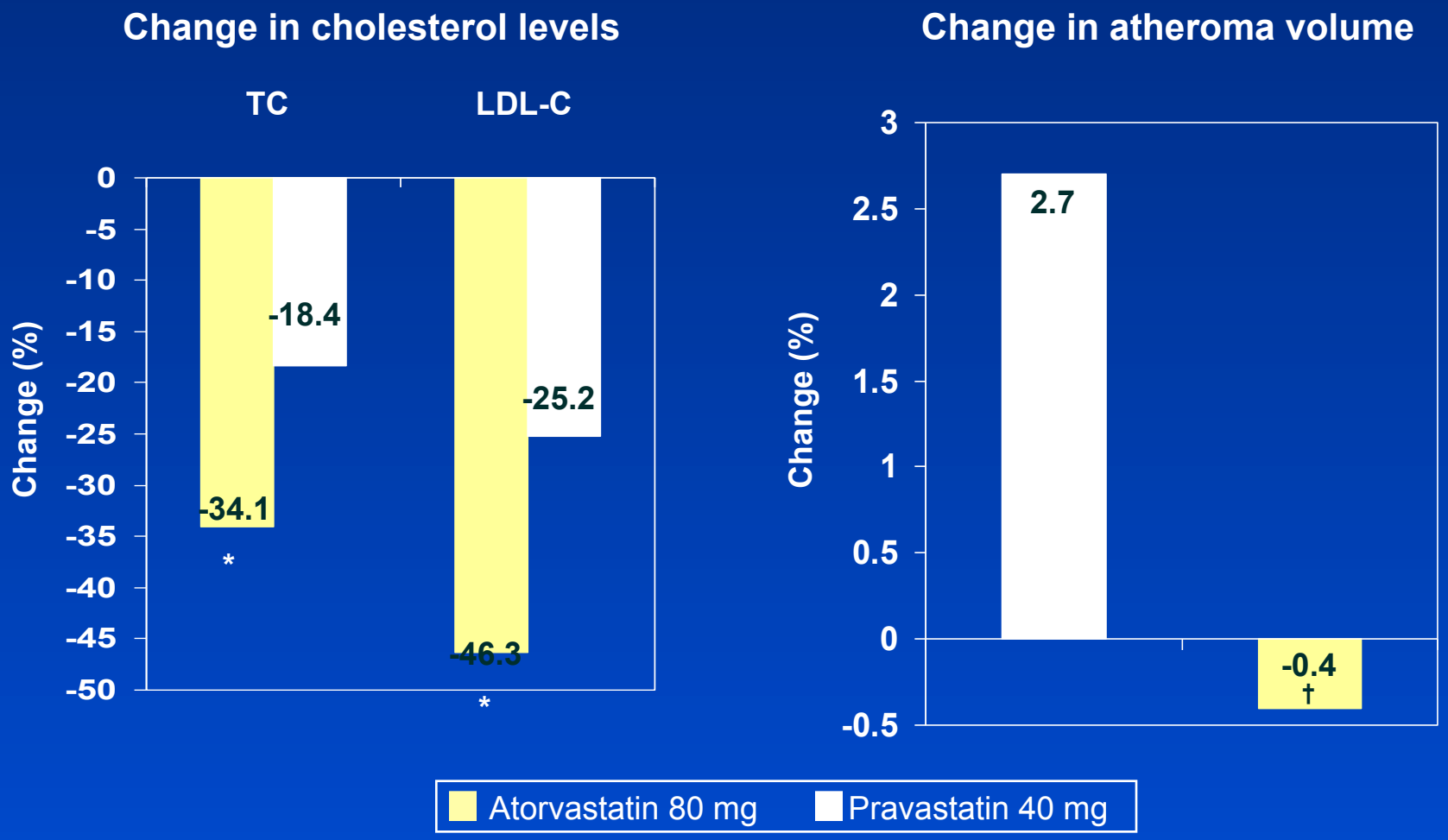
Nissen SE et al. *JAMA.* 2004;291:1071-1080.

REVERSAL: Quantification of Atheroma Volume With Intravascular Ultrasound (IVUS)



Nissen SE et al. *JAMA*. 2004;291:1071-1080.

REVERSAL: Greater Reductions in Cholesterol and Atheroma Volume With Atorvastatin Compared With Pravastatin

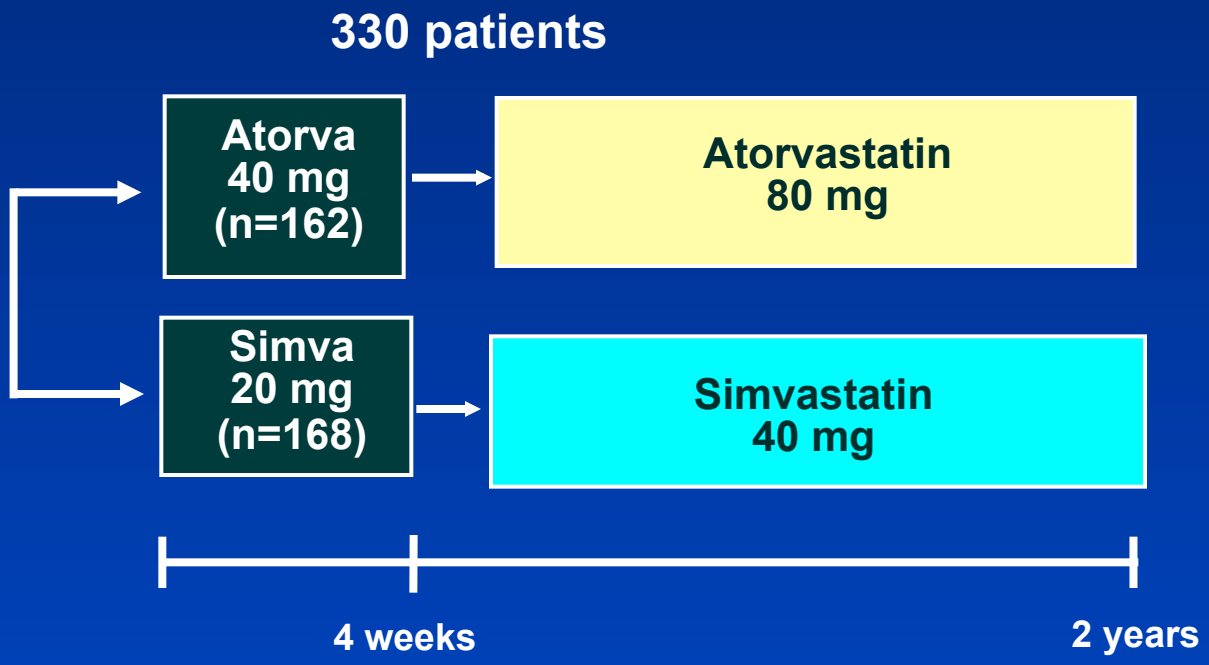


*P<.001 between groups.
†P =.02 between groups.
Nissen SE et al. *JAMA.* 2004;291:1071-1080.

Effect of Aggressive Versus Conventional Lipid Lowering on Atherosclerosis Progression in Familial Hypercholesterolemia (ASAP): Study Design

Patient population

- Men and women aged 30-70 years
- Familial hypercholesterolemia (FH)
- LDL-C >174.0 mg/dL



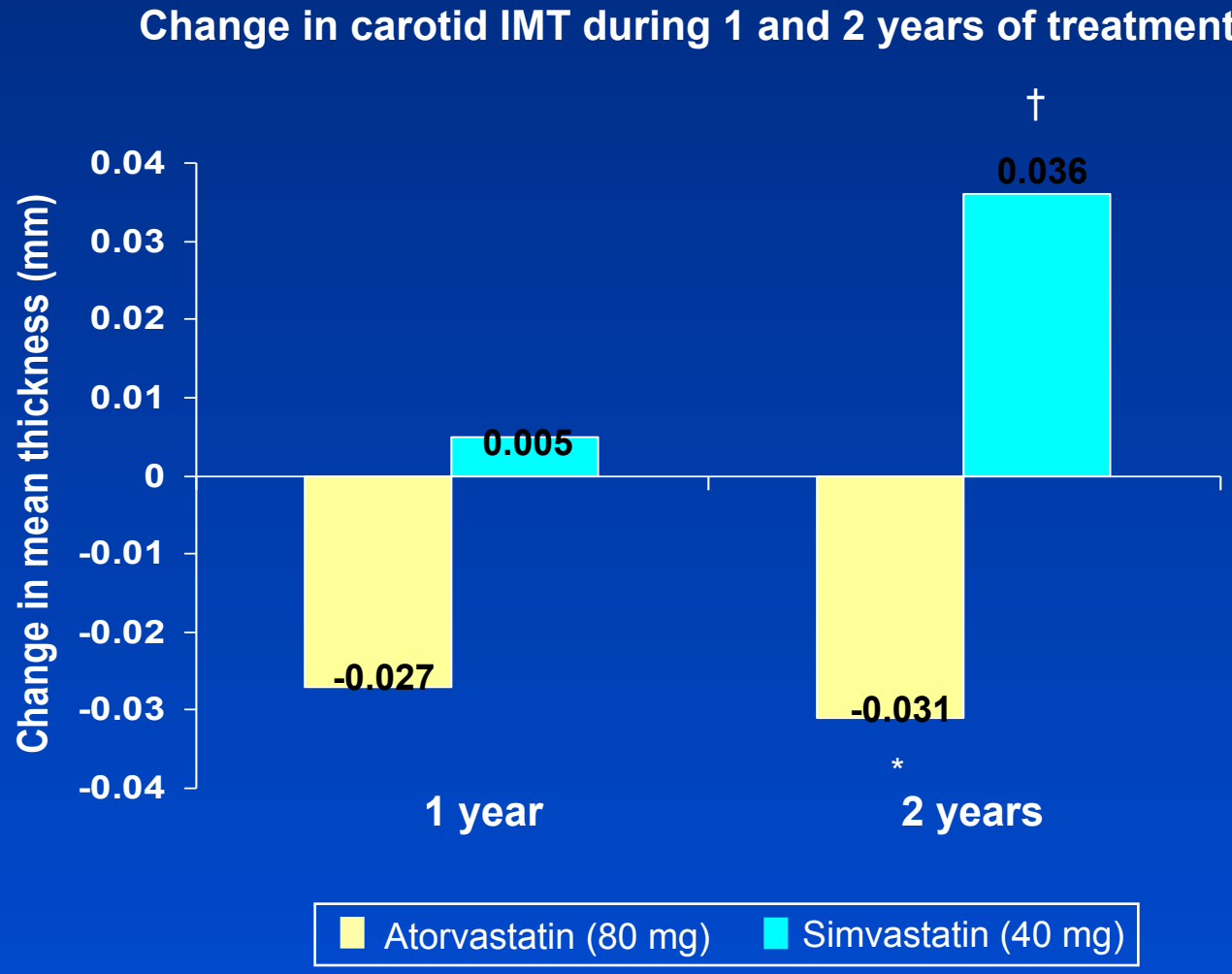
Primary efficacy end point

- Change in mean carotid IMT after 24 months

IMT=intima media thickness.

Smilde TJ et al. *Lancet.* 2001;357:577-581.

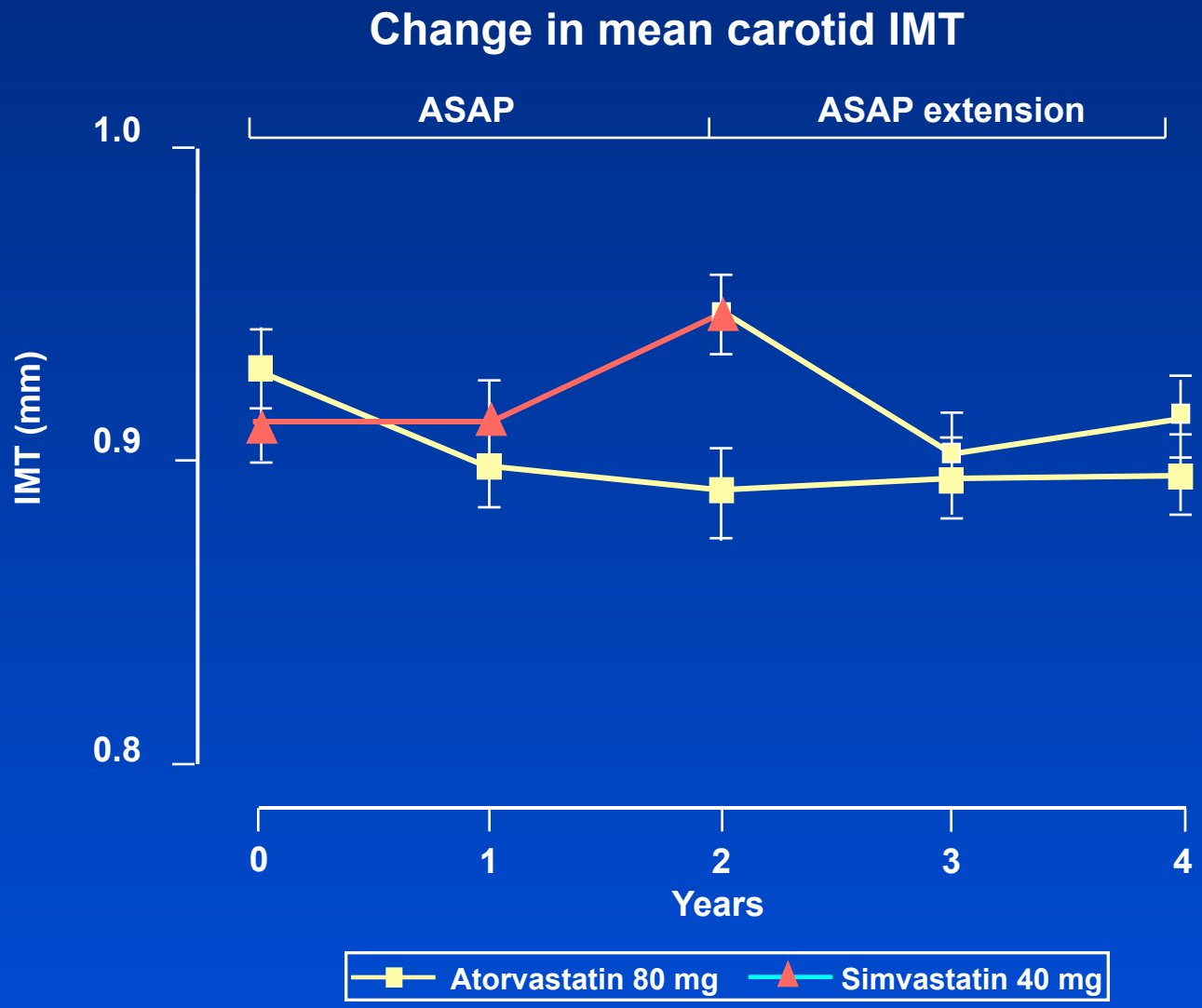
ASAP: Atorvastatin Superior to Simvastatin in Reducing Carotid IMT After 1 and 2 Years



*P=.00017; †P<.001.

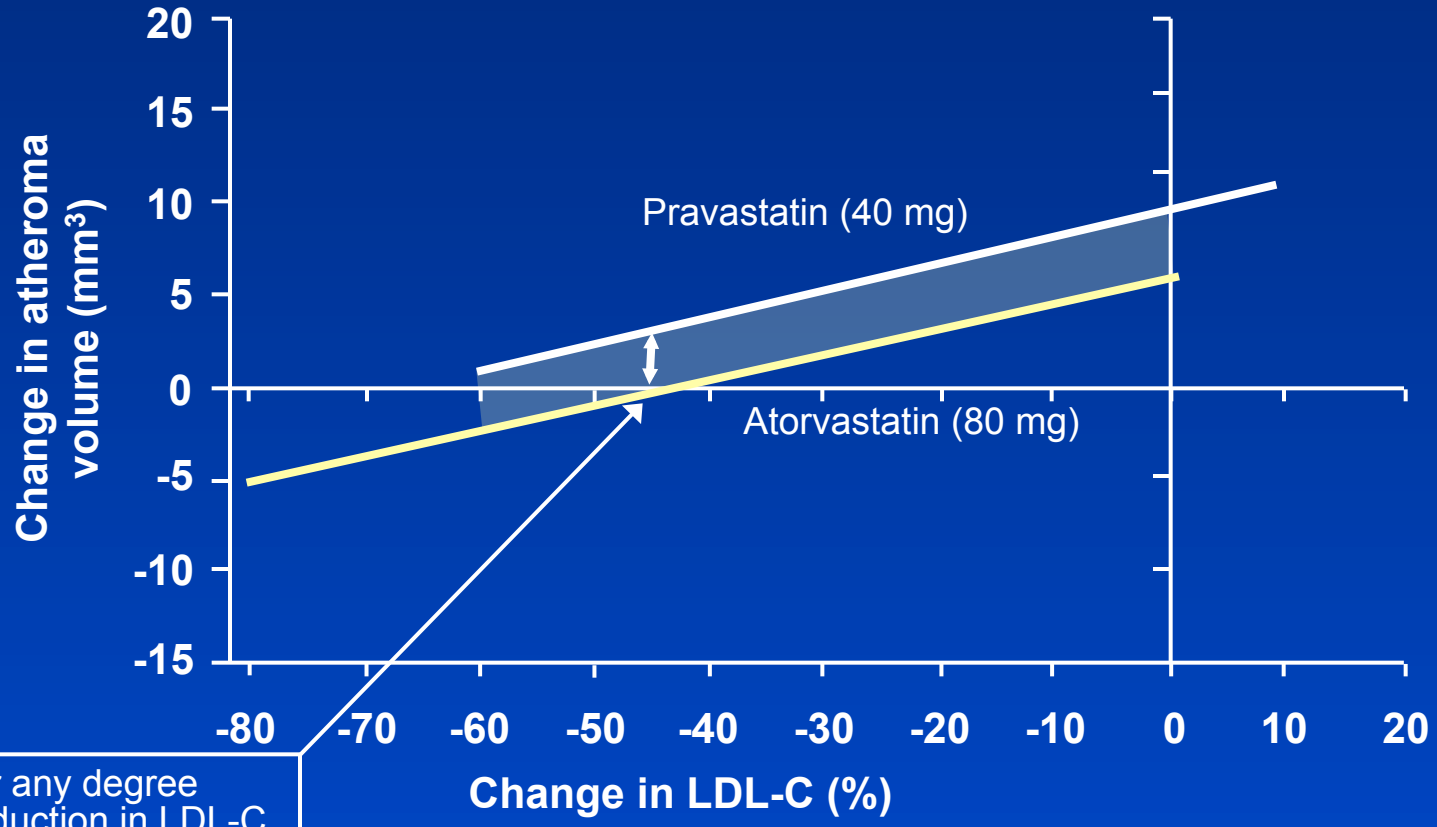
Smilde TJ et al. *Lancet*. 2001;357:577-581.

ASAP Extension Study: Long-term Treatment With Atorvastatin Achieved Complete Arrest of Carotid Atherosclerosis Progression



van Wissen S et al. *Am J Cardiol*. 2005;95:264-266.

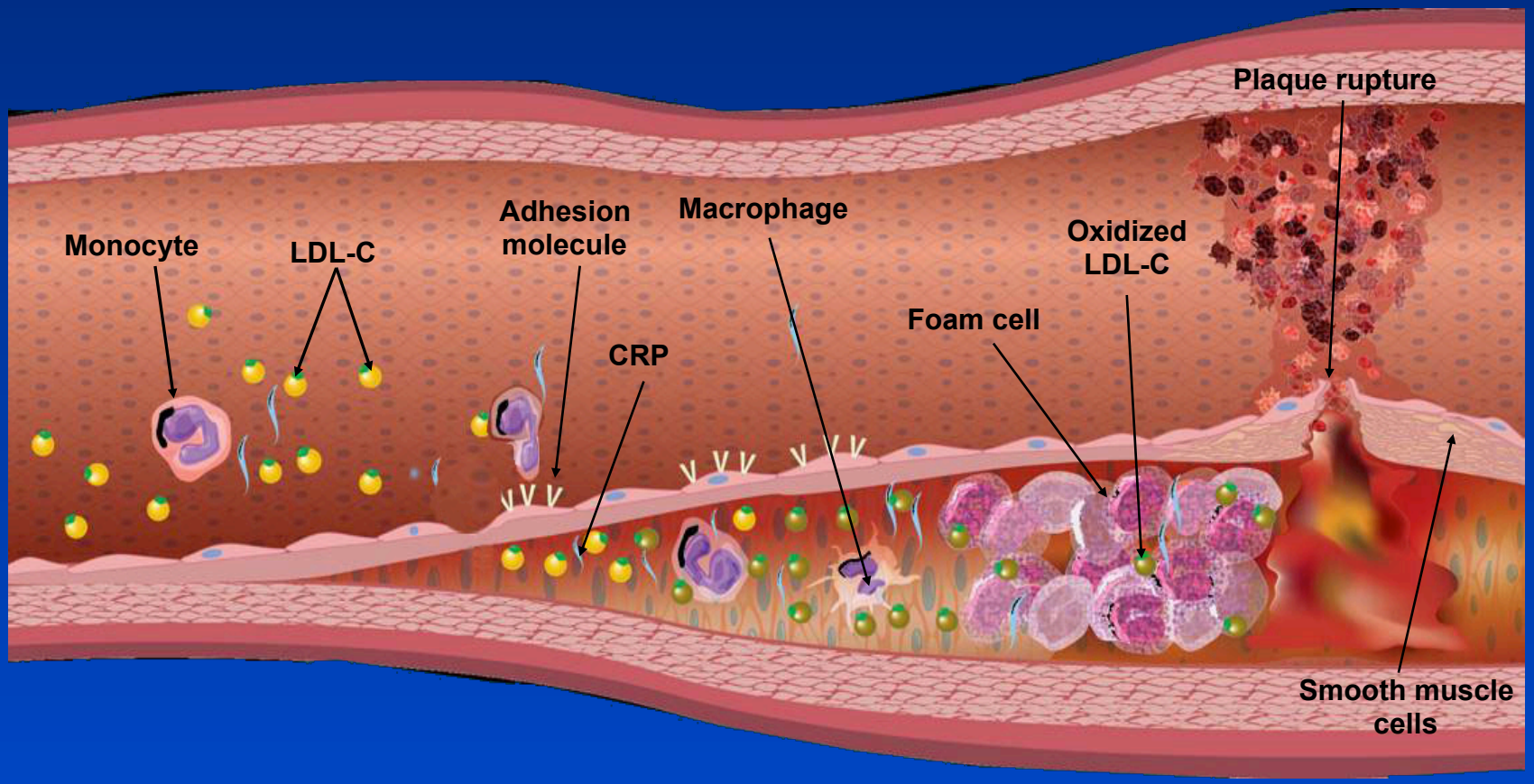
REVERSAL: Intensive Lipid Lowering With Atorvastatin Halted Plaque Progression After 18 Months



For any degree reduction in LDL-C, the progression rate was lower with atorvastatin than with pravastatin

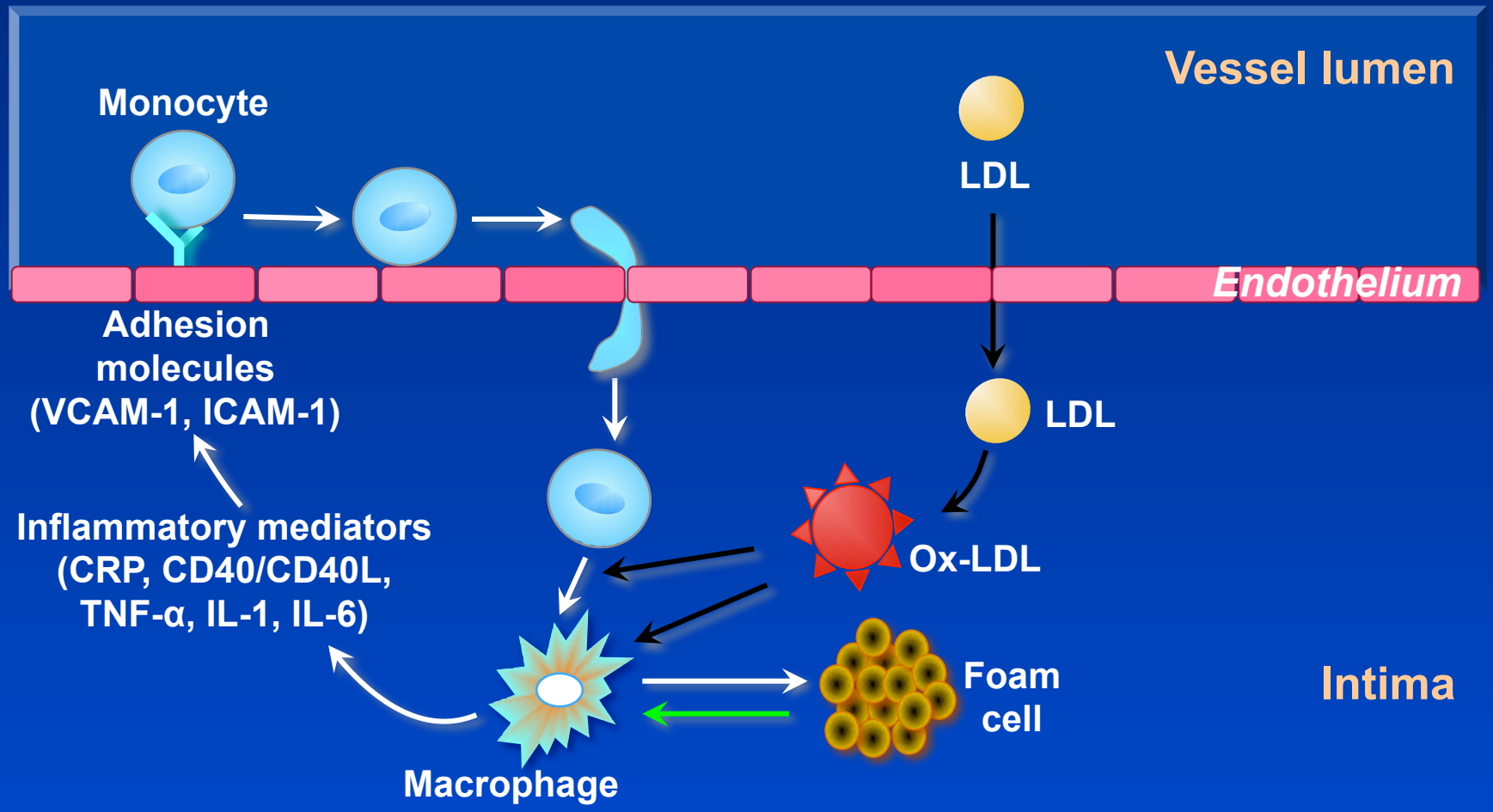
Nissen SE et al. *JAMA*. 2004;291:1071-1080.

Atherosclerosis Is an Inflammatory Disease



Libby P. *Circulation.* 2001;104:365-372; Ross R. *N Engl J Med.* 1999;340:115-126.

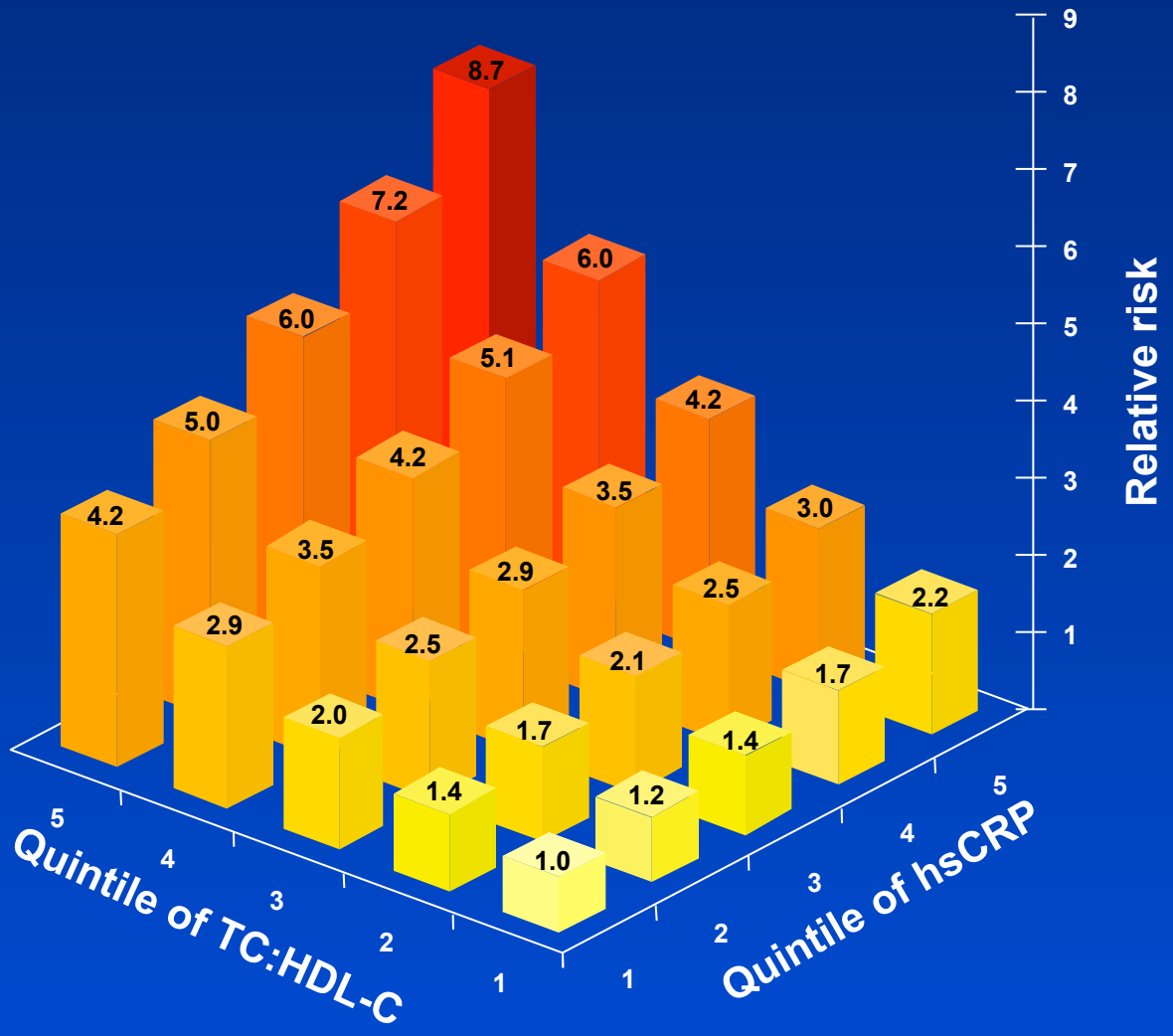
Inflammation Promotes Progression of Atherosclerosis



CD40L=CD40 ligand; TNF-α=tumor necrosis factor-alpha; IL=interleukin; VCAM=vascular cell adhesion molecule; ICAM=intercellular adhesion molecule.

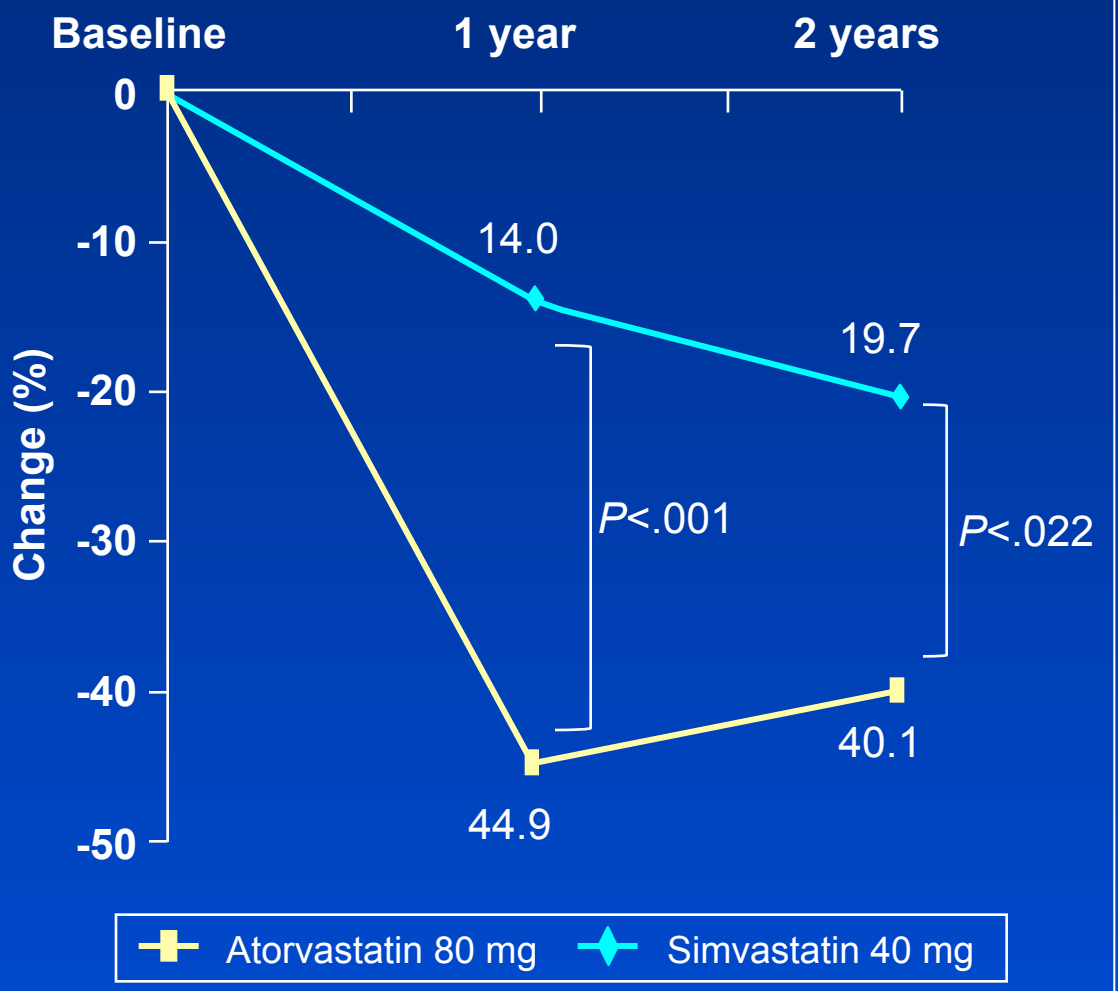
Cockerill GW et al. *Arterioscler Thromb Vasc Biol.* 1995;15:1987-1994; Andre P et al. *Circulation.* 2002;106:896-899; Libby P. *Circulation.* 2001;104:365-372; Libby P et al. *Circulation.* 2002;105:1135-1143; Ross R. *N Engl J Med.* 1999;340:115-126.

CRP Is a Predictor of Cardiovascular Disease



Ridker PM. *Circulation.* 2001;103:1813-1818; Libby P et al. *Circulation*. 2002;105:1135-1143.

ASAP: Atorvastatin Reduced CRP to a Greater Extent Than Simvastatin

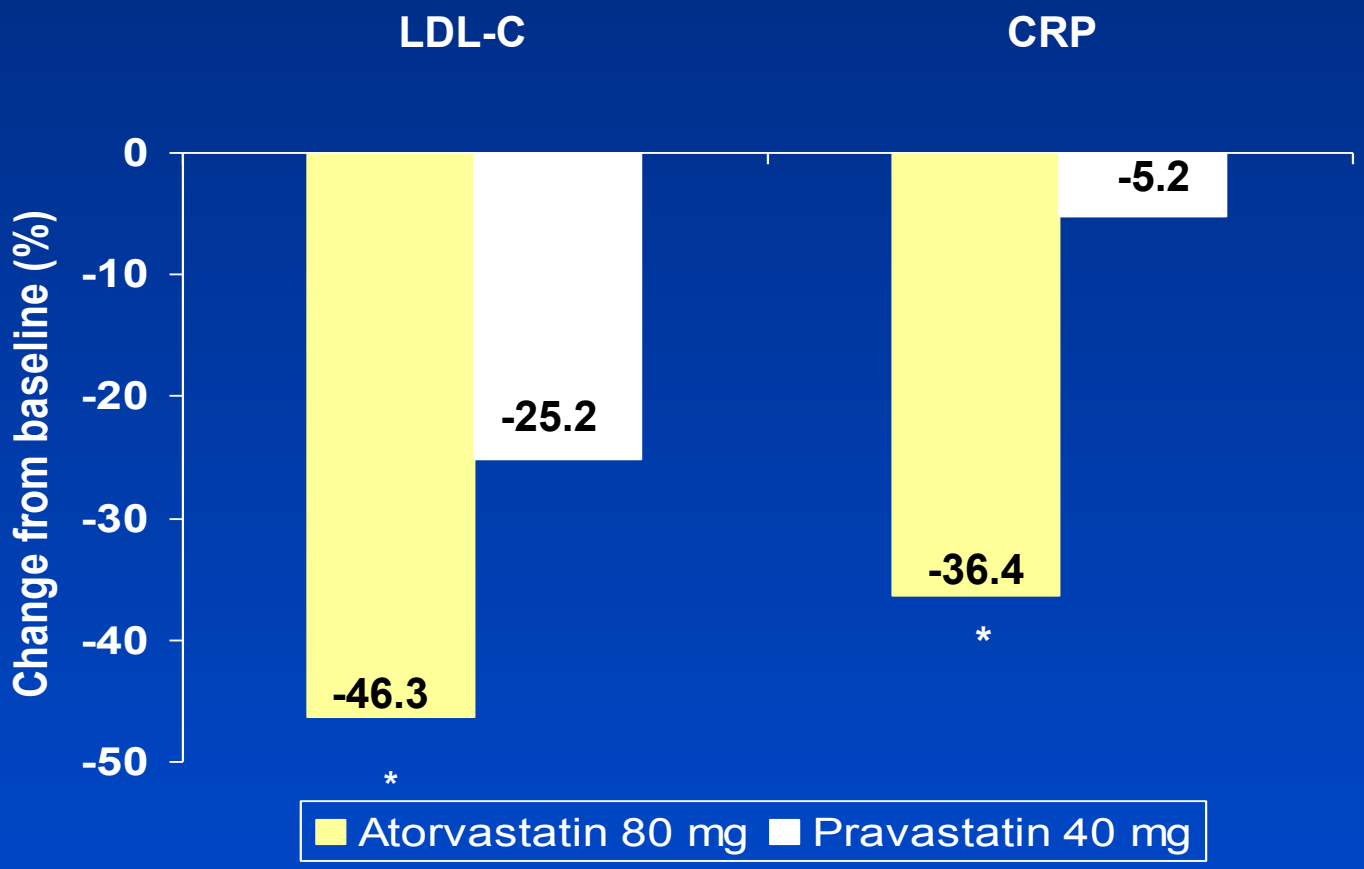


Additional Findings

- **No correlation between CRP and LDL-C reduction**
- **Significant correlation between decrease in CRP and reduction in IMT (r =.13; P=.03)**
- **Patients in the highest tertile of change in CRP had the greatest mean reduction in IMT**

van Wissen S et al. *Atherosclerosis.* 2002;165:361-366.

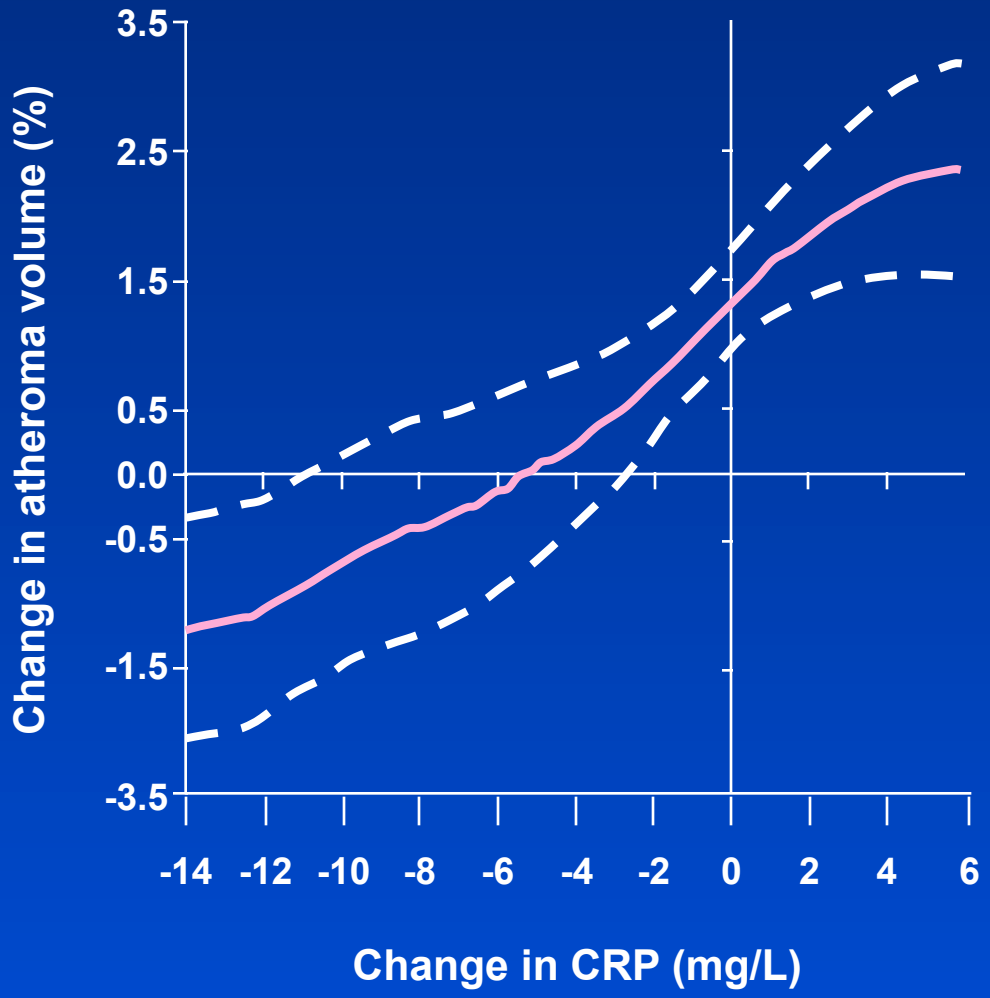
REVERSAL: Greater Reductions in LDL-C and CRP With Atorvastatin Compared With Pravastatin



*P<.001.

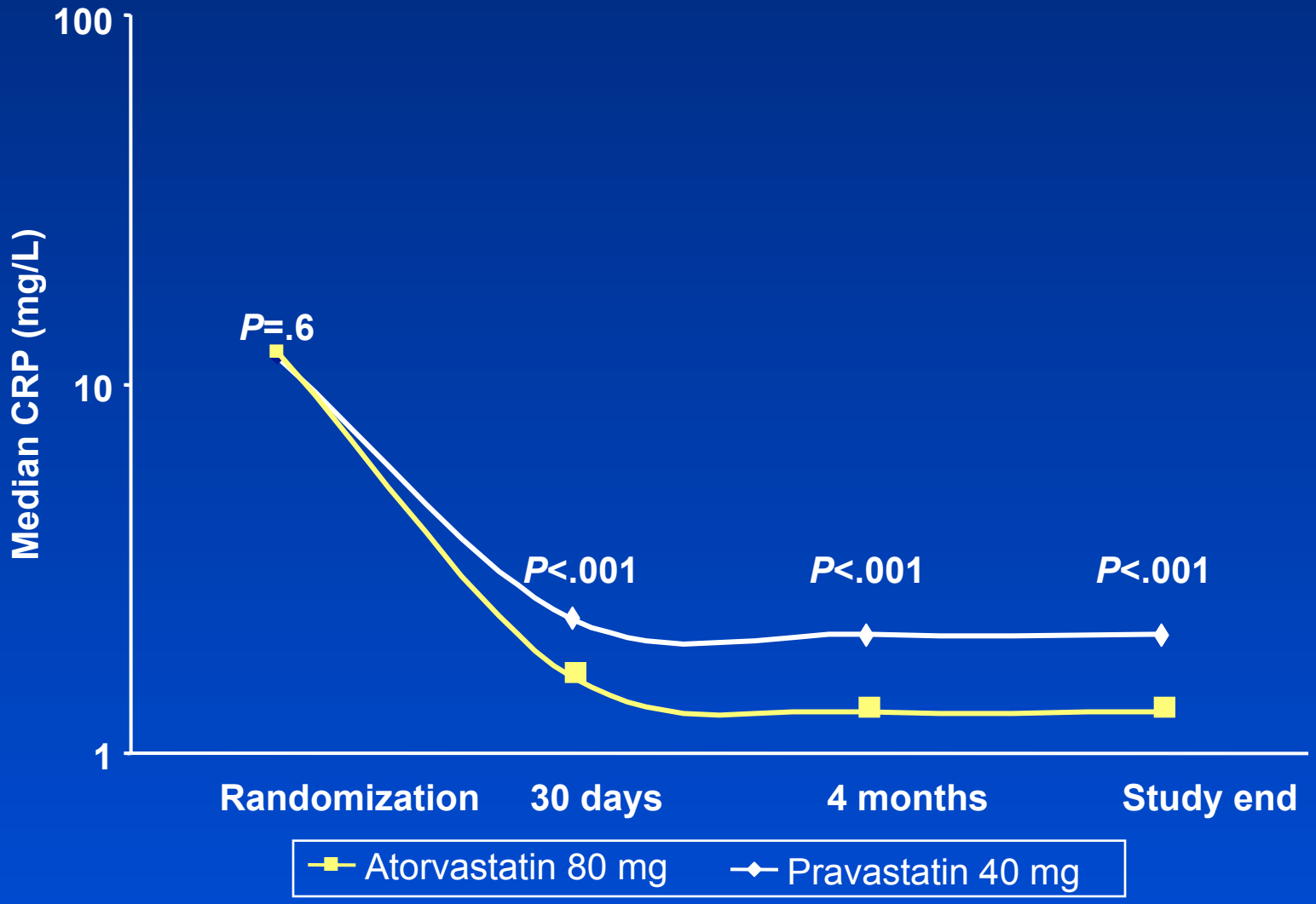
Nissen SE et al. *JAMA*. 2004;291:1071-1080.

REVERSAL: Reductions in CRP Correlated With Reductions in Atheroma Volume



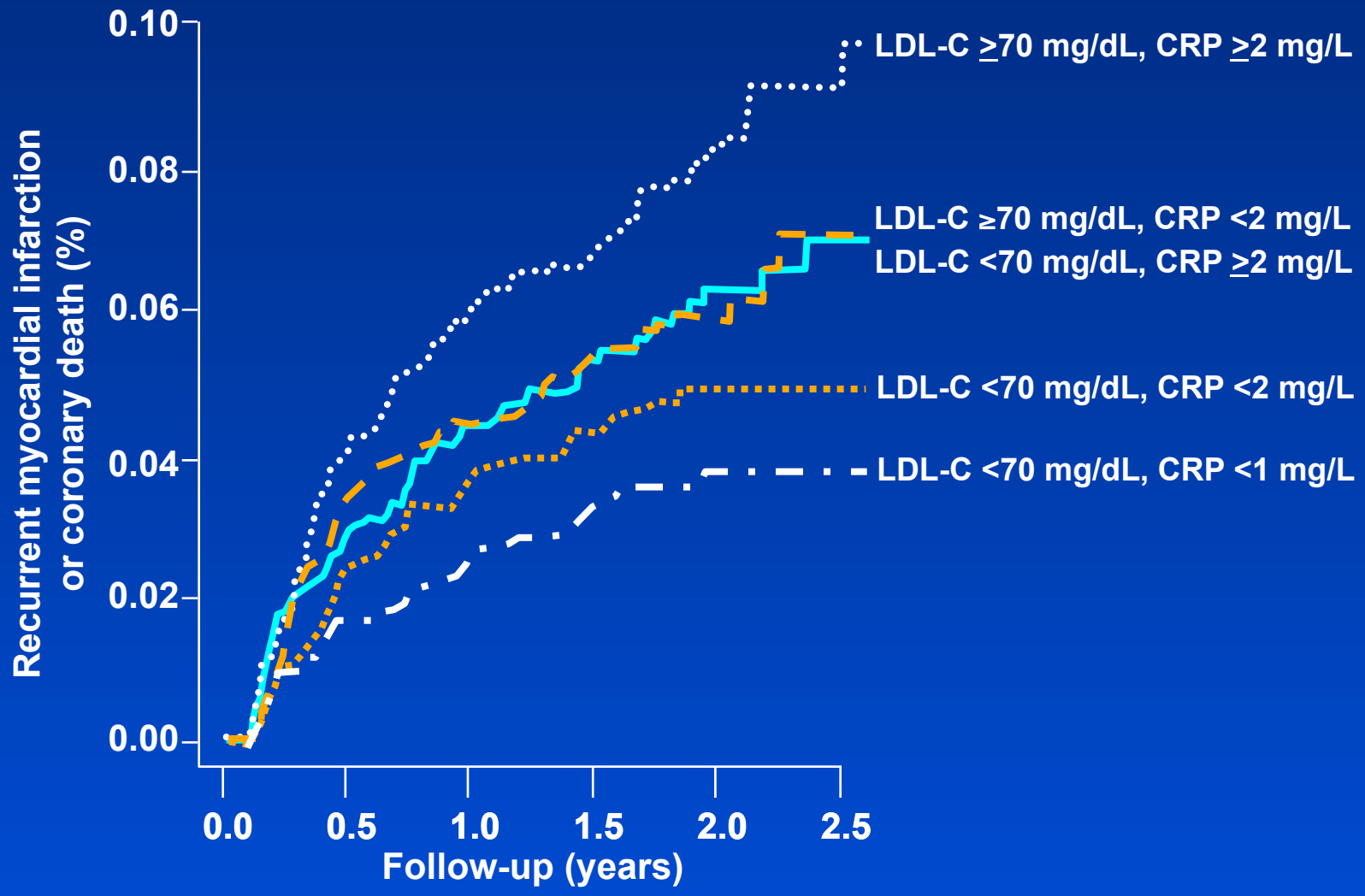
Nissen SE et al. *N Engl J Med*. 2005;352:29-38.

PROVE IT: Greater Reductions in CRP With Atorvastatin



Ridker PM et al. *N Engl J Med*. 2005;352:20-28.

PROVE IT: Patients With the Lowest Levels of LDL-C and CRP Experienced Fewer Recurrent Events



Adapted from Ridker PM et al. *N Engl J Med*. 2005;352:20-28; Ridker PM et al. Presented at AHA Scientific Sessions; 2004.

Atorvastatin Provided Greater CRP Reductions in Patients With ACS

	A to Z	MIRACL	PROVE IT
Treatment	**Simva (40-80 mg) vs placebo + simva 20 mg**	**Atorva 80 mg vs placebo**	**Atorva 80 mg vs prava 40 mg**
No. of patients randomized	**4497**	**3086**	**4162**
LDL-C differential (mg/dL)			
Early*	**62**	**63**	**33**
Late	**15**	**NA**	**28**
CRP differential (%)	**17**	**34**	**38**
Event reduction (%)			
Early	**0***	**16***	**18†**
Late‡	**11**	**NA**	**16**

*Measured 120 days after randomization.
†Measured 90 days after randomization.
‡Measured at trial completion—24 months in A to Z and PROVE IT.

Nissen SE. *JAMA*. 2004;292:1365-1367; de Lemos et al. *JAMA*. 2004;292:1307-1316; Cannon CP et al. *N Engl J Med*. 2004;350:1495-15504.