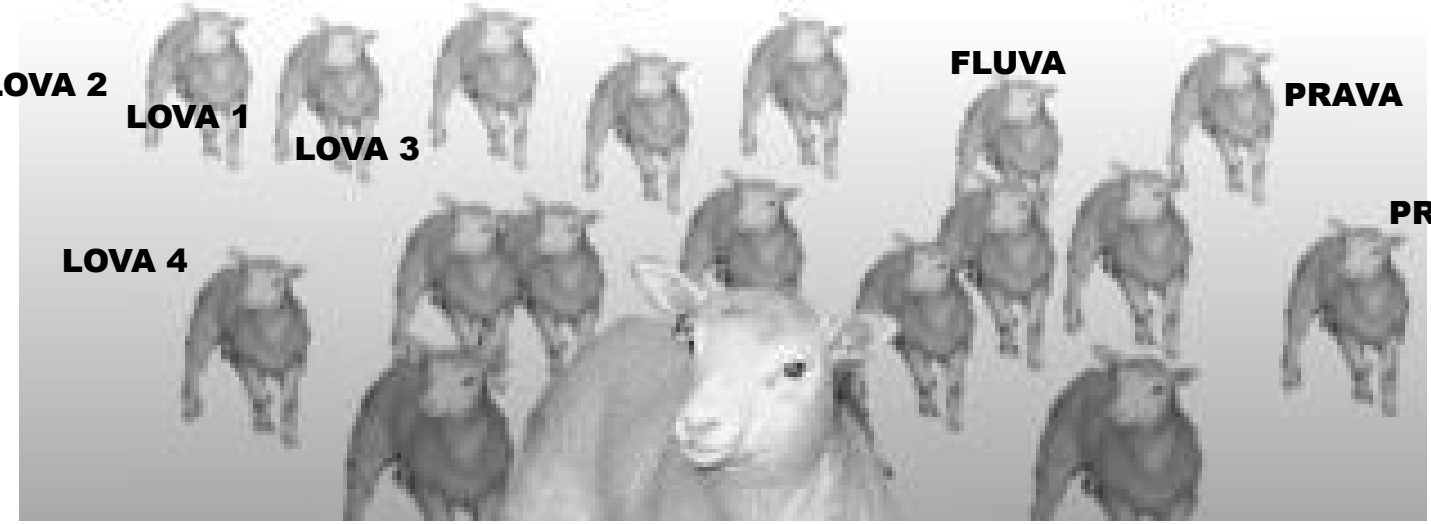
Pleiotropic effects of Statin

Ki Hoon Han
Asan Medical Center
Seoul Korea

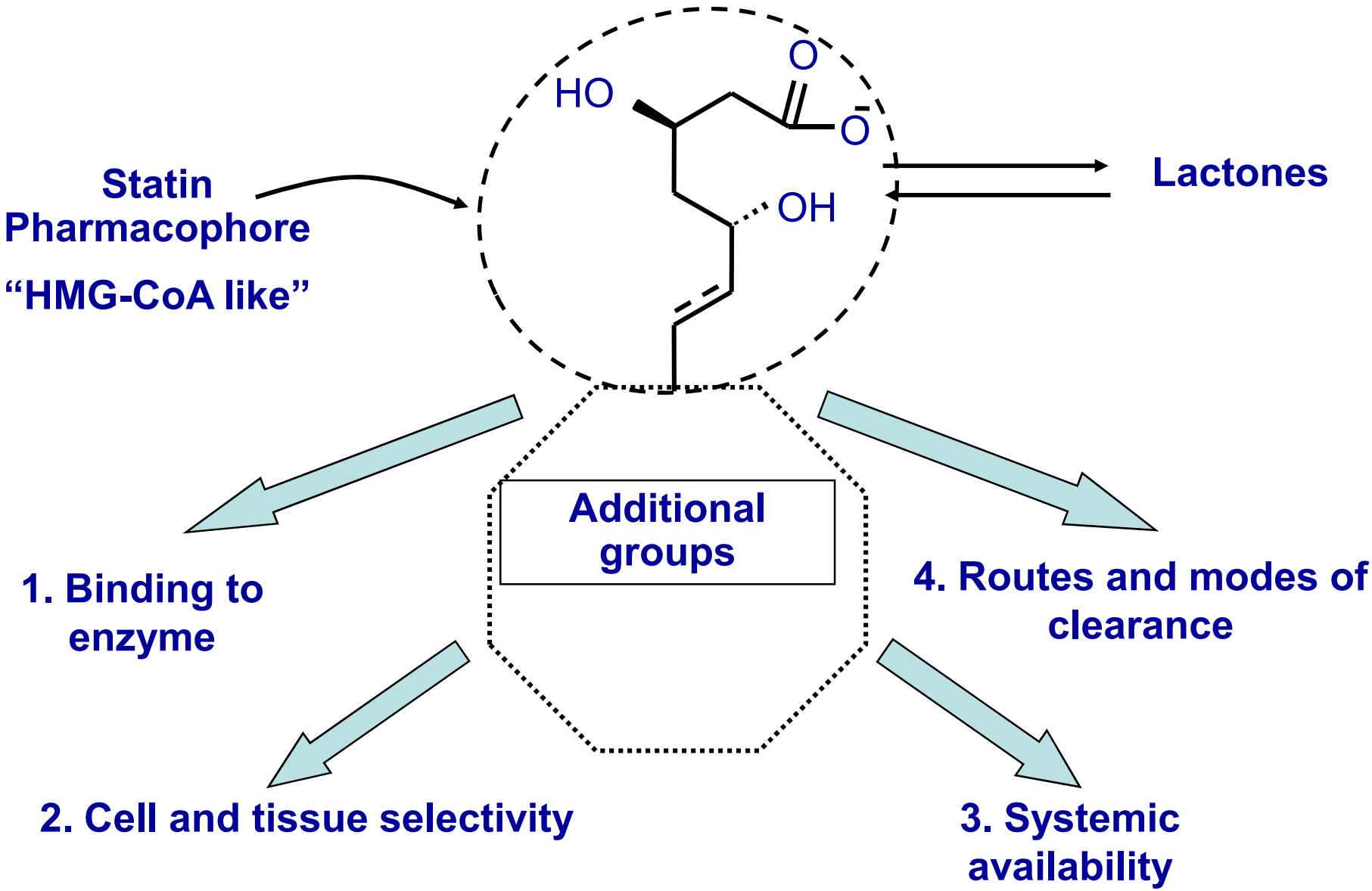
CERIVA

STATIN WARS

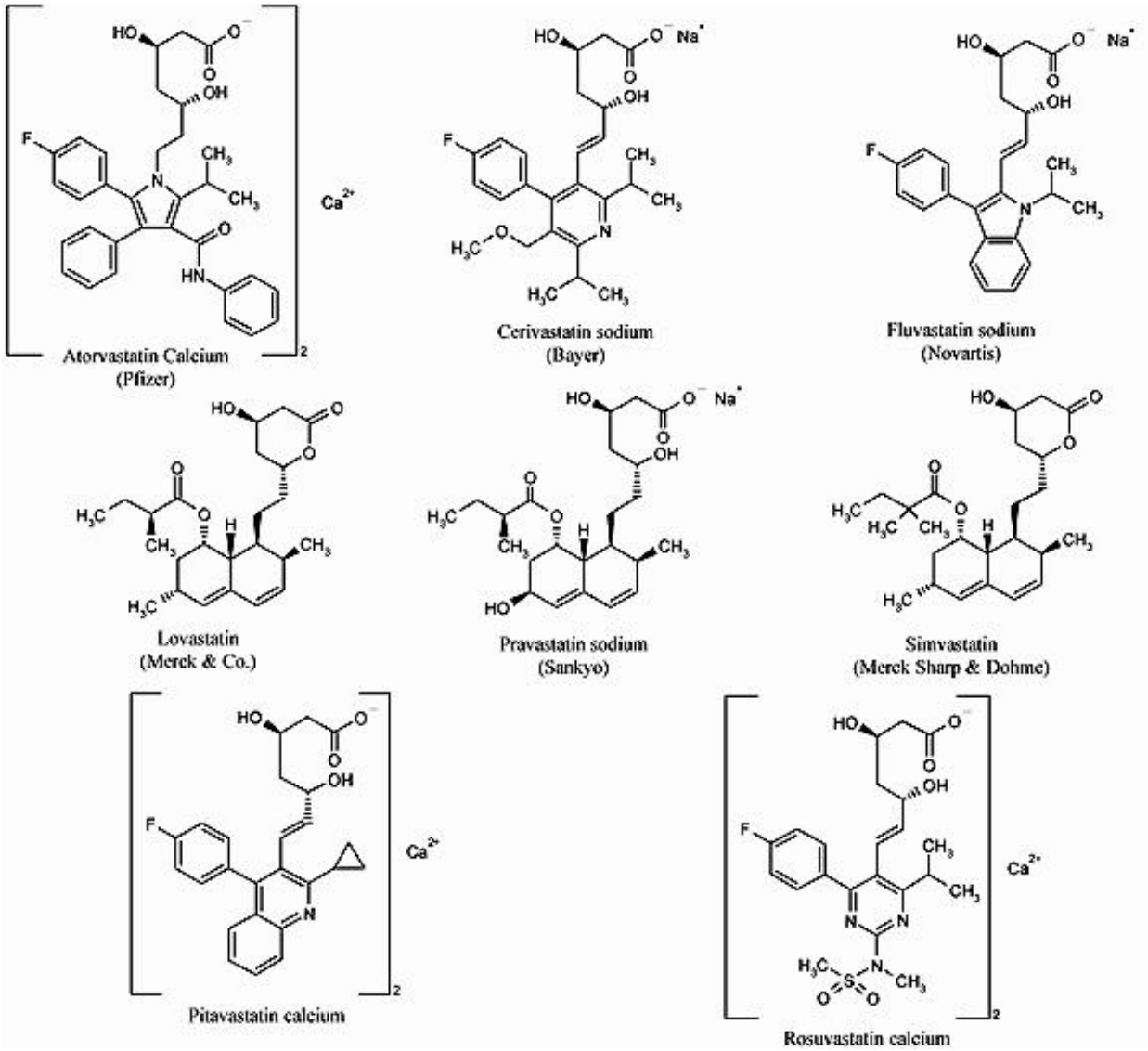
ATTACK OF THE CLONES



Structure of Statins



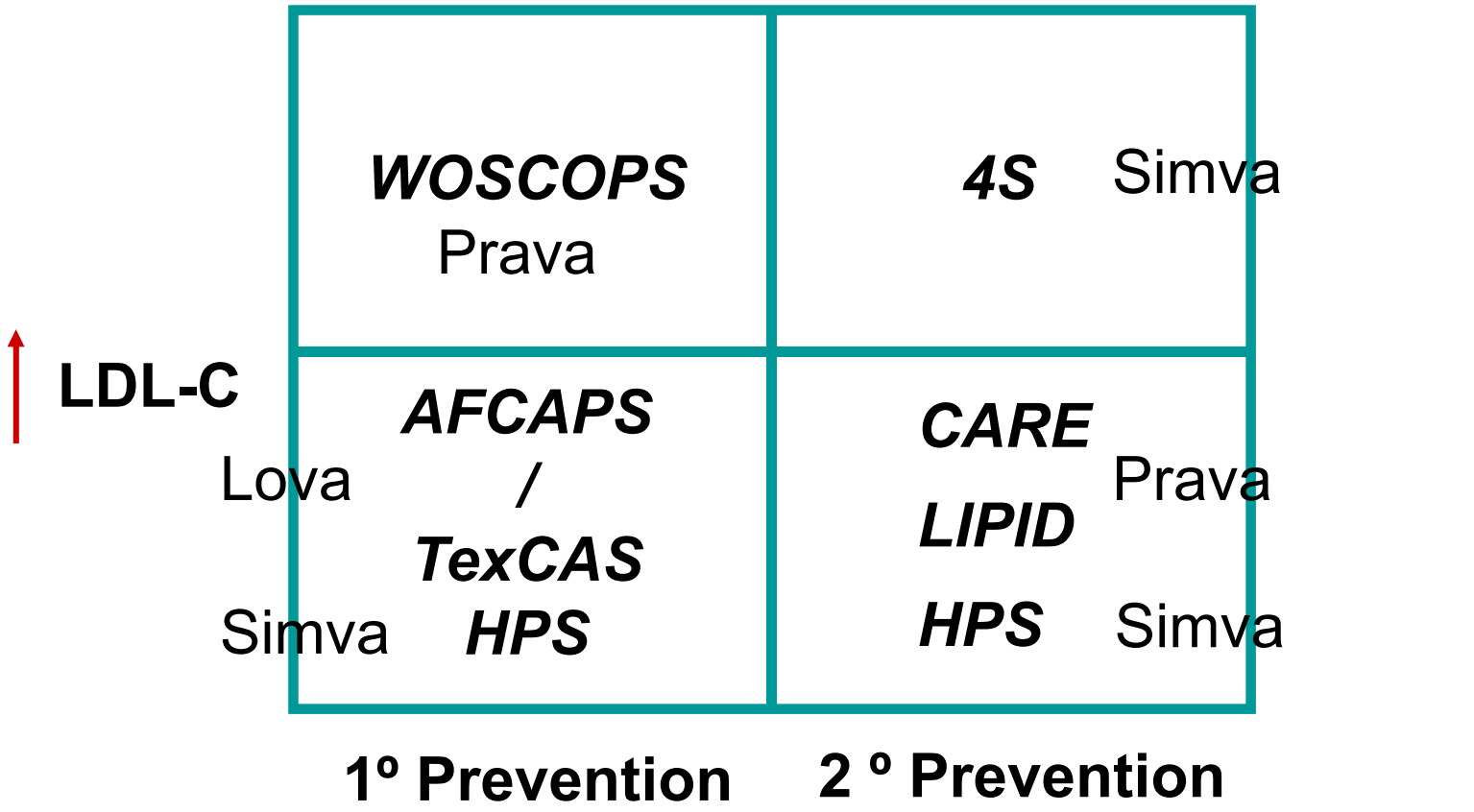
Opened lactone ring = active form



Statins

- Inactive form = lovastatin, simvastatin
- Longer half life = rosuvastatin, atorvastatin, pitavastatin
- Lowest renal excretion = atorvastatin
- Higher bioavailability = water soluble statins and pitavastatin

Major Statin Trials



Gotto, et al. AHA Nov '97

Downs, et al JAMA.1998;279: 1615 - 22

30 % LDLc reduction, 30 % CVD prevention

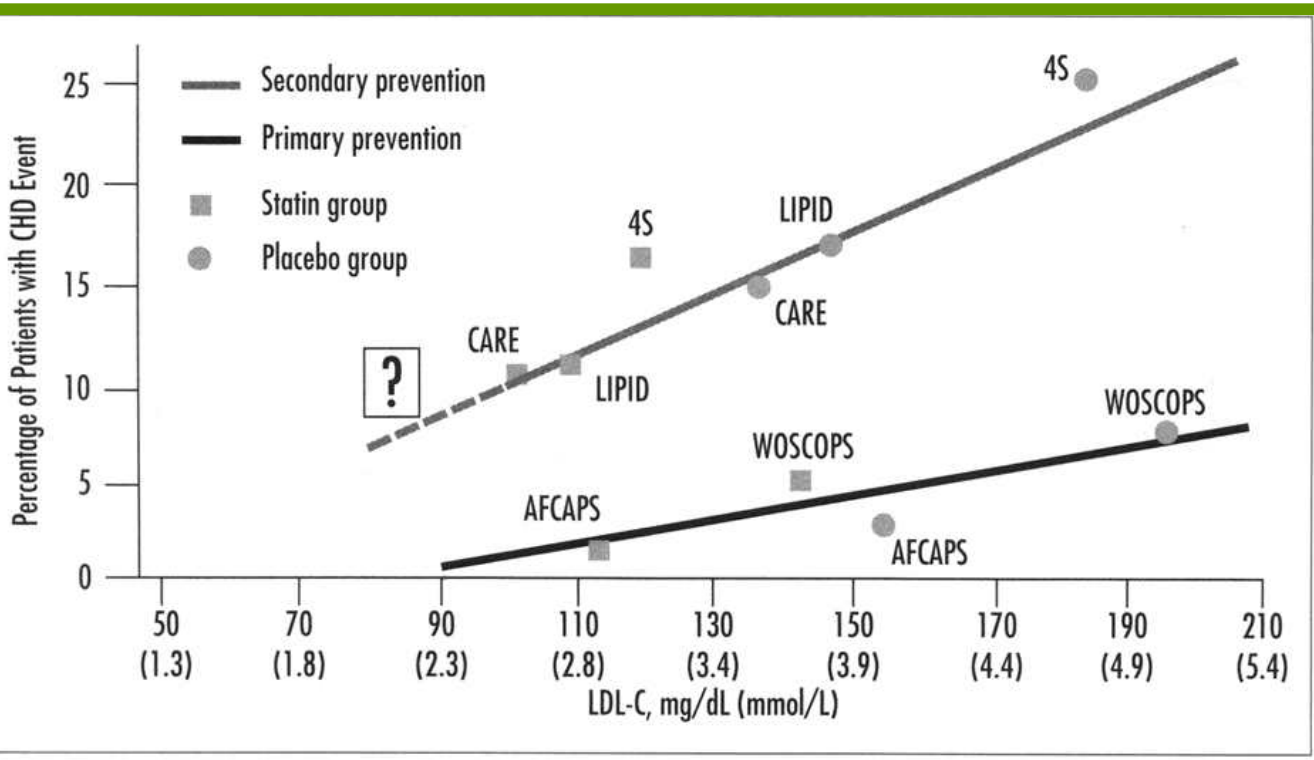
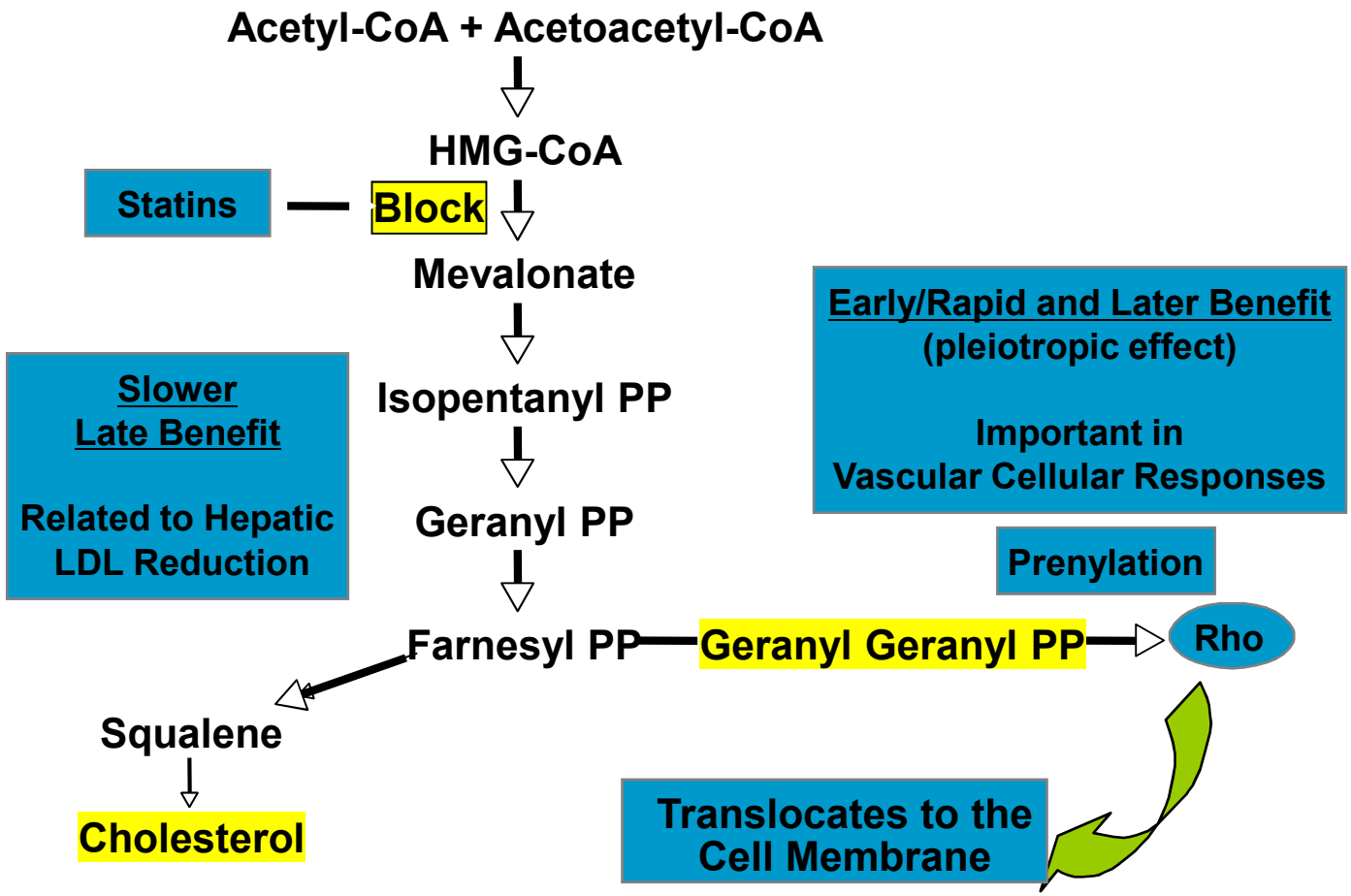


Figure 1.5-2. Hypothesis of the Treating to New Targets (TNT) trial. The ongoing secondary-prevention TNT trial is directly examining whether "lower is better" in cholesterol lowering to reduce CHD events. Patients with initial LDL-C 130–230 mg/dL (3.4–5.9 mmol/L) and TG ≤600 mg/dL (≤6.8 mmol/L) who achieve LDL-C <130 mg/dL (<3.4 mmol/L) after 8 weeks of diet and atorvastatin 10 mg/day are randomized to double-blind therapy with atorvastatin 10 or 80 mg/day (respective targets, ≤100 and ≤75 mg/dL, or ≤2.6 and ≤1.9 mmol/L). WOSCOPS, CARE, and LIPID tested pravastatin, 4S simvastatin, and AFCAPS/TexCAPS lovastatin as cholesterol-lowering therapy (see text for full names of trials). Modified from Kastelein JJP. The future of best practice. *Atherosclerosis* 1999;143(suppl 1):S17–S21; used with permission.

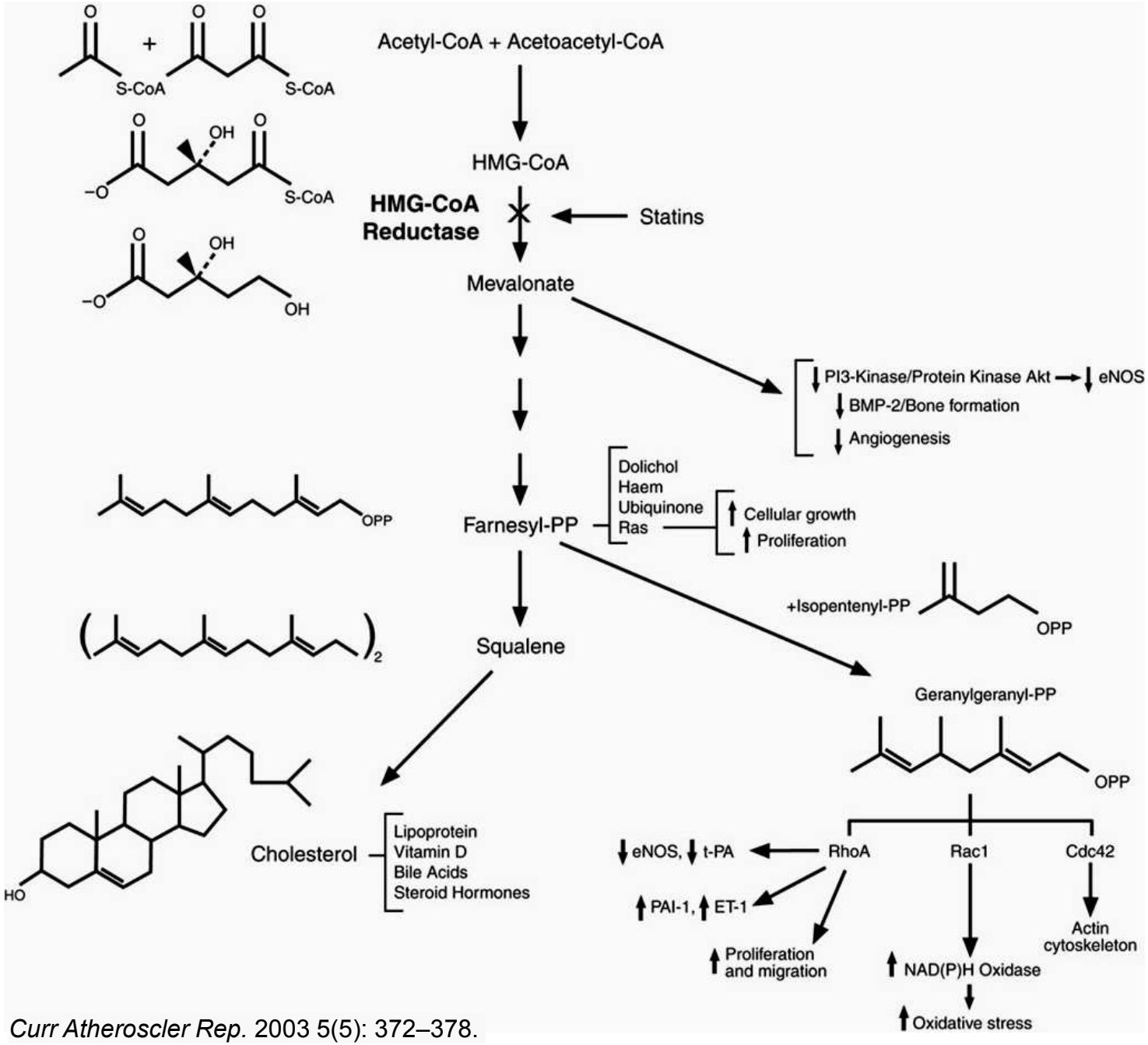
Metabolic Pathways Blocked By Statins



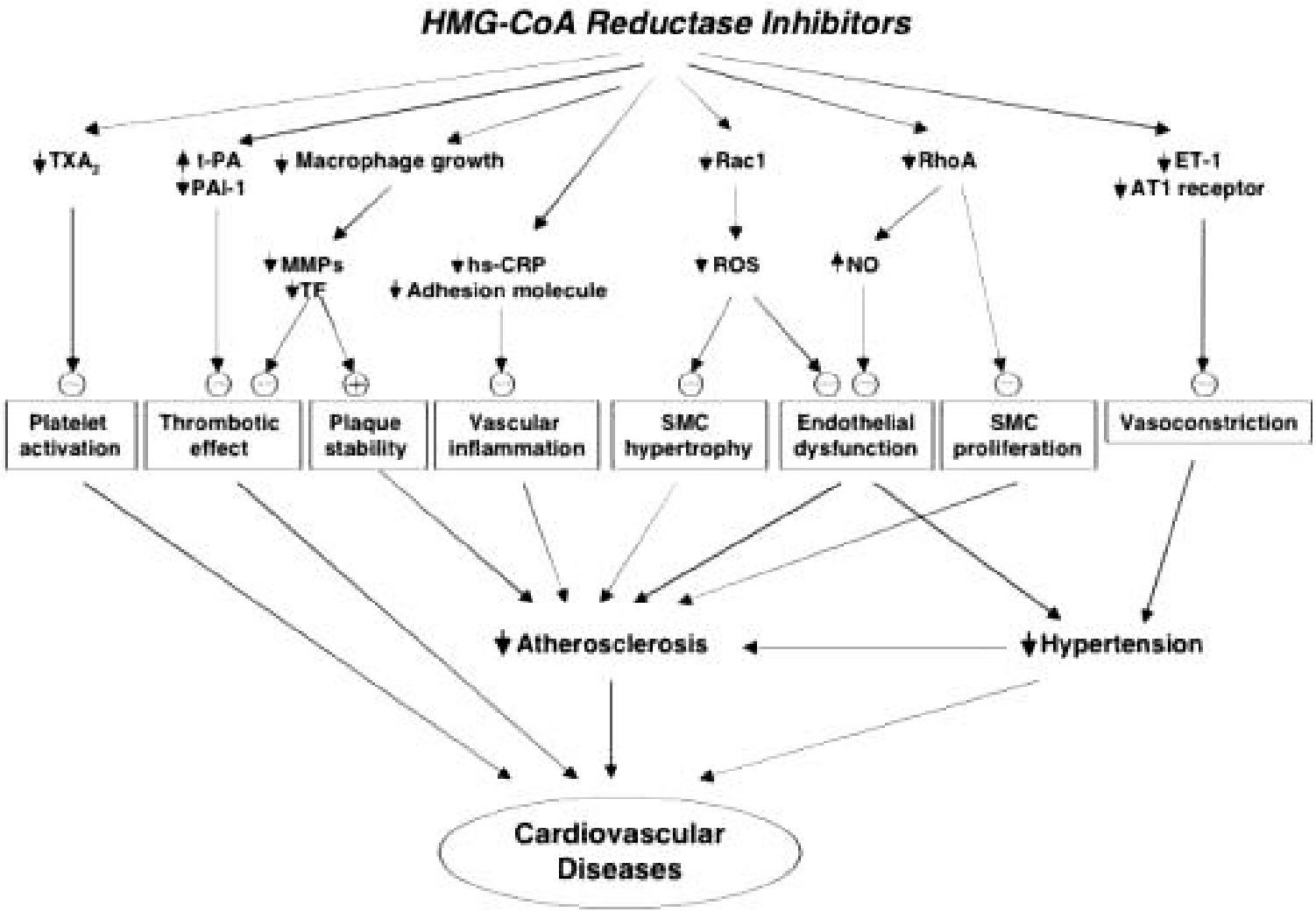
PP = pyrophosphate.

Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

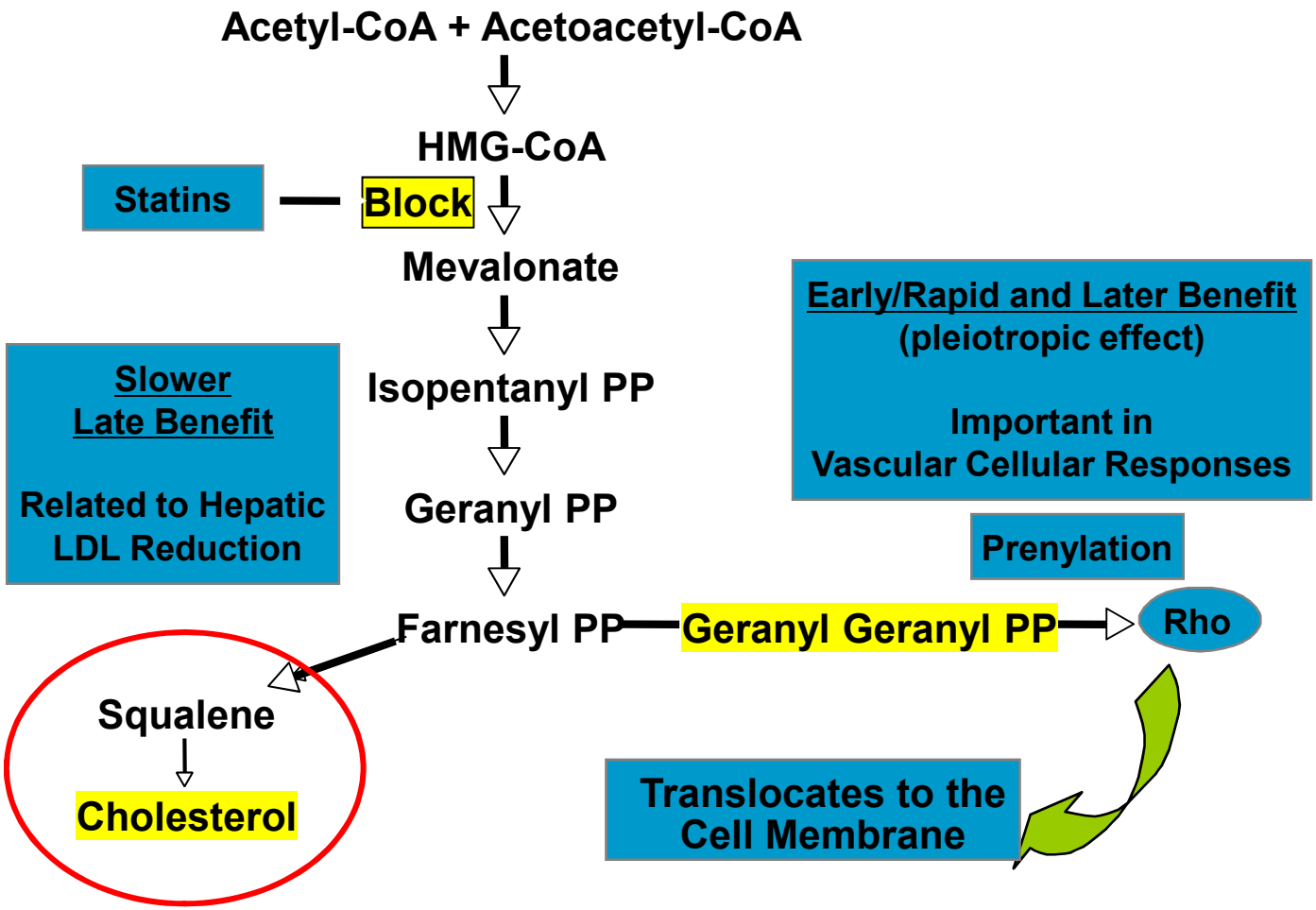


Curr Atheroscler Rep. 2003 5(5): 372–378.



Curr Atheroscler Rep. 2003 5(5): 372–378.

Metabolic Pathways Blocked By Statins



PP = pyrophosphate.

Reproduced from Ray and Cannon. *Curr Opin Lipidol*. 2004;15:637, with permission.

Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

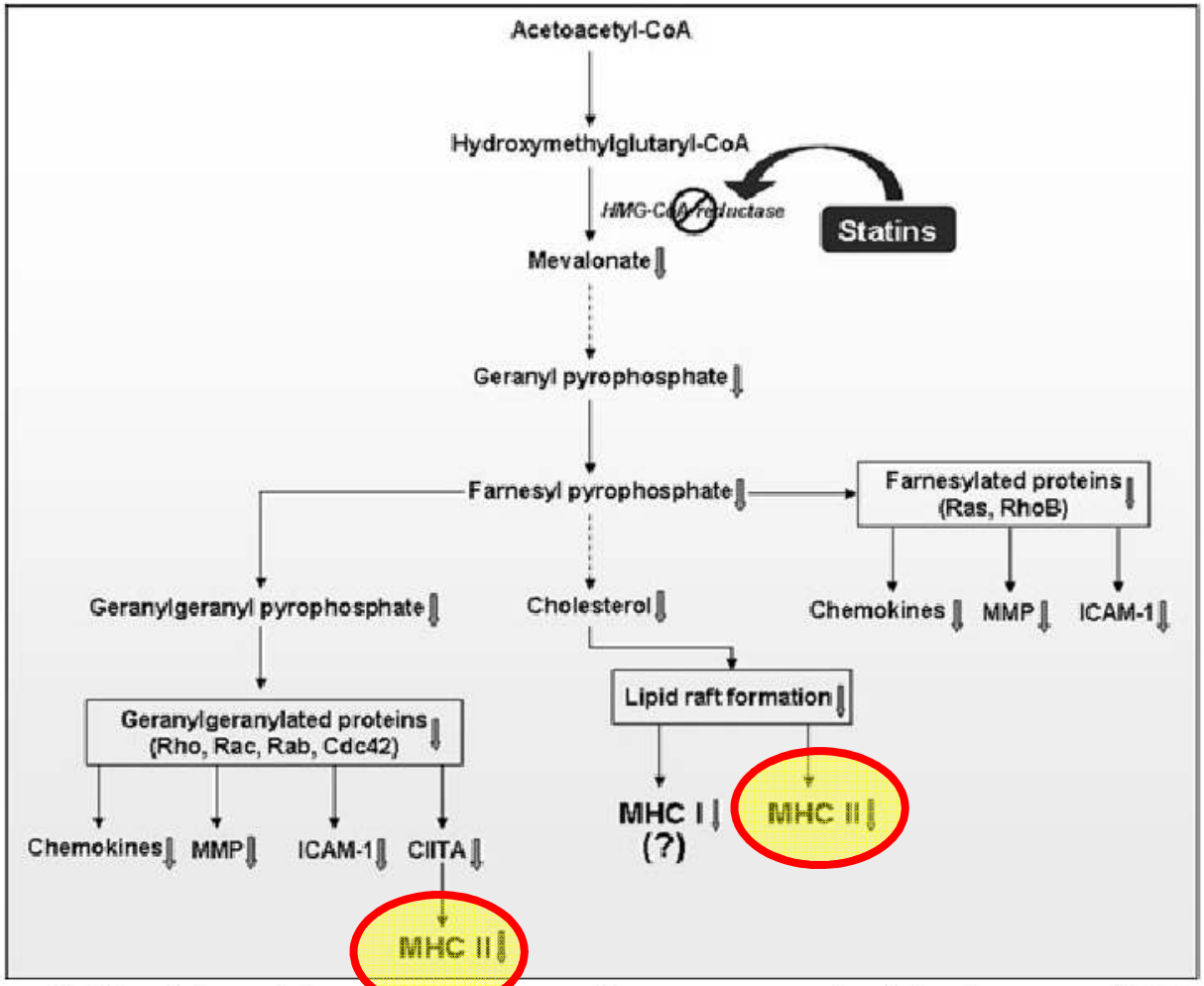


Figure 1. The cholesterol biosynthesis pathway. Statins competitively inhibit the enzyme HMG-CoA reductase, thus inhibiting the synthesis of mevalonate, which leads to decreased production of cholesterol and isoprenoid intermediates. As isoprenoid compounds are important for posttranslational modification of proteins like GTPases, statins affect a number of processes in a cell. These effects include inhibition of inducible MHC class II expression, inhibition of co-stimulatory molecules, a shift from Th1 to Th2 phenotype, reduction in expression of cell adhesion molecules and cell motility, etc. Less cholesterol impairs the lipid raft formation and thus has its effect on expression of molecules on cell surface and also on cell proliferation.

Ann. N.Y. Acad. Sci. 1173: 746–751 (2009).
CIITA ; class II transactivator

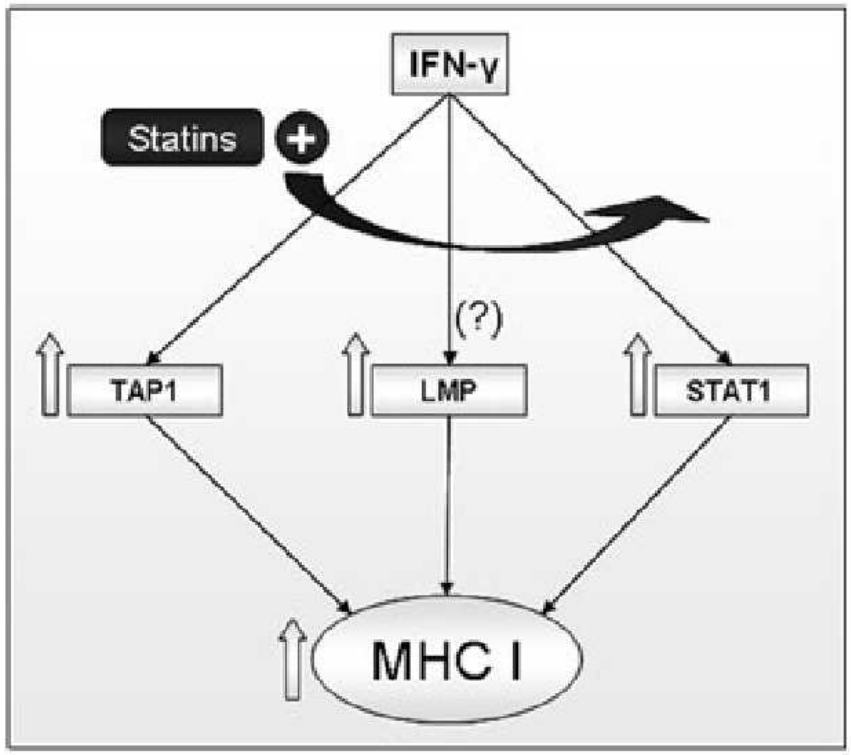


Figure 2. A proposed scheme for statins' effect on MHC class I expression. Statins might affect cytokine induced expression of STAT1 and the expression of proteins involved in class I antigen presentation (TAP and LMP). It has been shown that they attenuate IFN-γ–induced STAT1 activation in endothelial cells.

Ann. N.Y. Acad. Sci. 1173: 746–751 (2009).
TAP; transporter associated with antigen processing family
LMP; low molecular mass polypeptide

Immuno-modulatory effects of statins

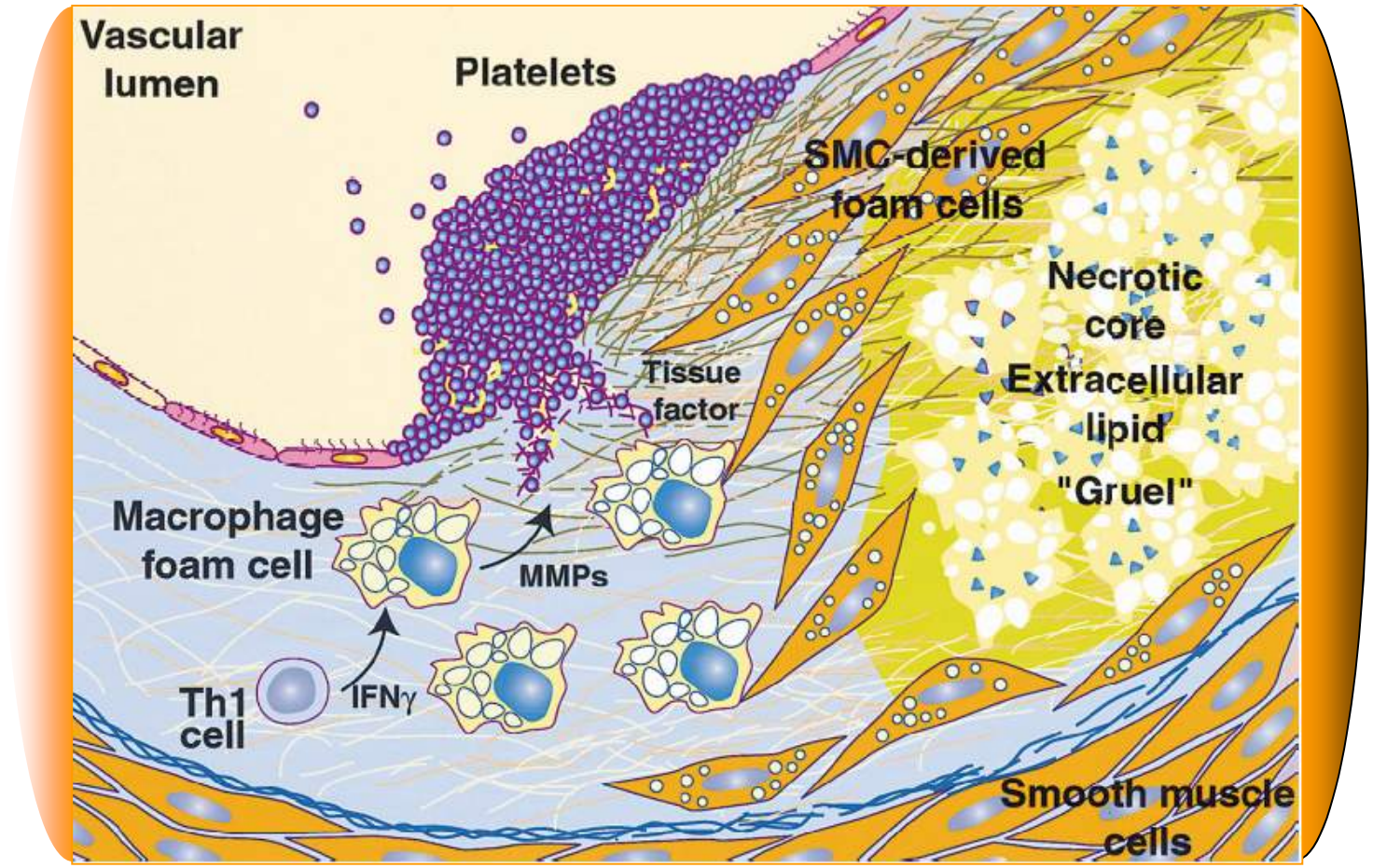
- Inhibition of cytokine-inducible NO synthase expression
- Interference with non-antigen-specific T cell proliferation
- Inhibition of T-cell adhesion and infiltration of the target organ
- Shit from Th1 to Th2 cytokines
- Reduced co-stimulatory molecules
- Downregulation of IFN-gamma-inducible MHC class I and II expression

Ann. N.Y. Acad. Sci. 1173: 746–751 (2009).

Statin shows clear benefit in ACS

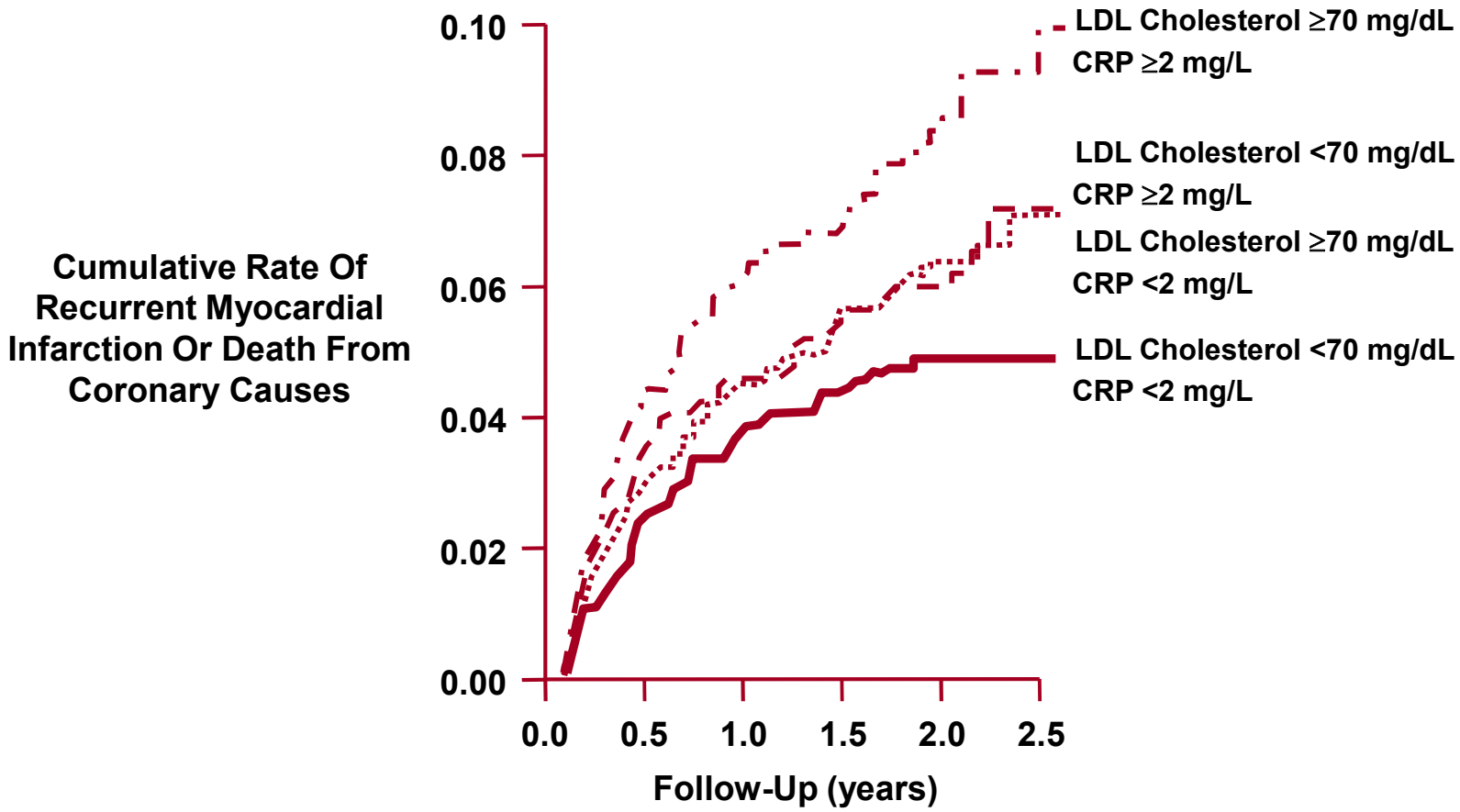
ACS ; atherogenesis + inflammation

Plaque Rupture



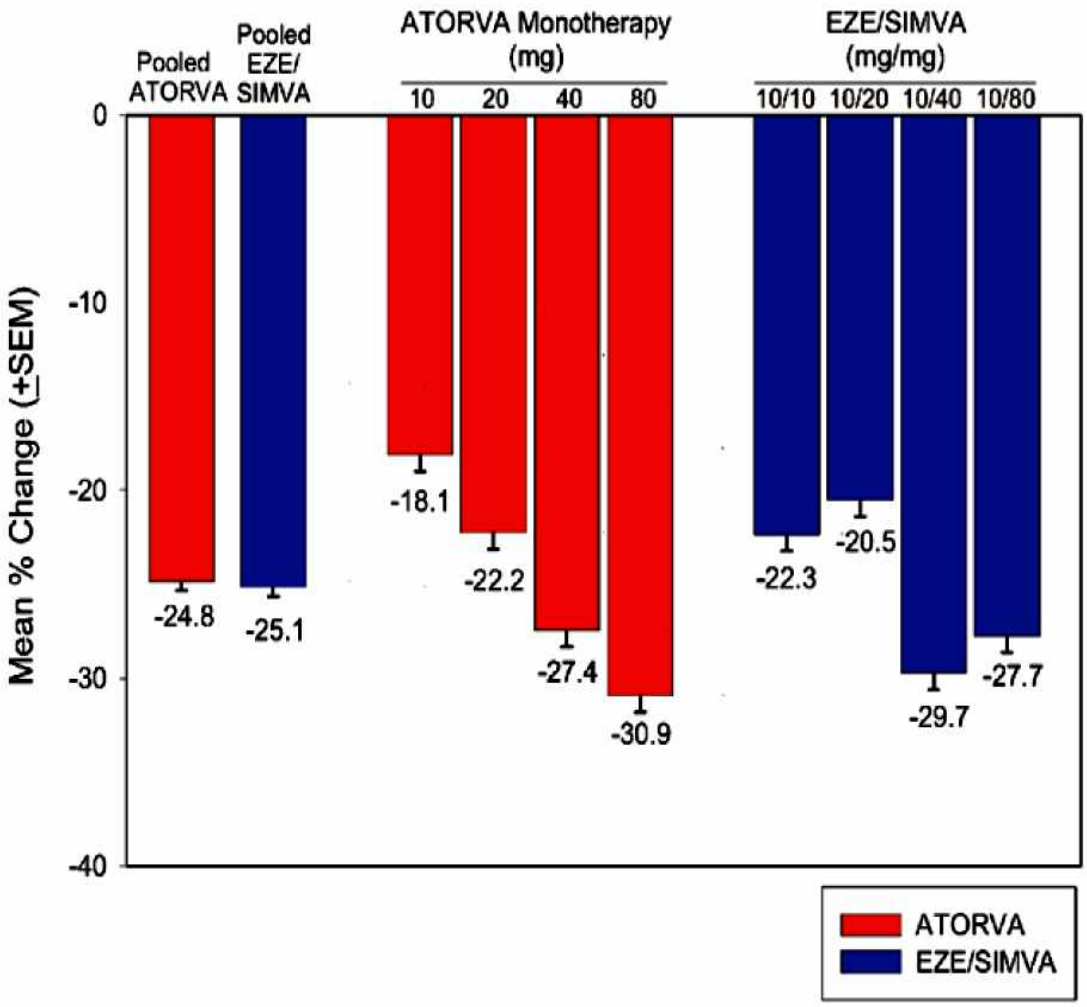
Glass,K and Witztum, JL Cell 2001 104:513-516

PROVE IT-TIMI 22: Prognostic Value Of 30-Day Achieved LDL And CRP On Recurrent MI Or Death From Cardiovascular Causes



Reproduced from Ridker et al. *N Engl J Med*. 2005;352:20, with permission.
Ray and Cannon. *Am J Cardiol*. 2005;96(suppl):54F.

Atorva and Eze/Simva Had Similar Reductions in CRP at Each mg-Equivalent Statin Dose Comparison



Pearson T et al. Am J Cardiol 2007;99:1706–1713

ARMYDA trio ;
more myocardial salvage by
early intensive statin treatment

- **ARMYDA ;**
  - N=153, stable angina
    40mg/d atorva 7d prior to PCI
- **ARMYDA-ACS ;**
  - N=191, ACS
    80mg, 40mg atorva 12H, 2H prior to PCI
- **ARMYDA-RECAPTURE ;**
  - N=352, ACS or angina, Hx of statin>30d,
    80mg, 40mg atorva 12H, 2H prior to PCI

Role of Statins in ACS (and angina before PCI)

- Lowering ‘Bad cholesterol’ (LDL) to <70 mg/dl
  - LDL may be just a marker

- Lowering inflammatory burden (hCRP <2 mg/L)

  - revascularization is important !

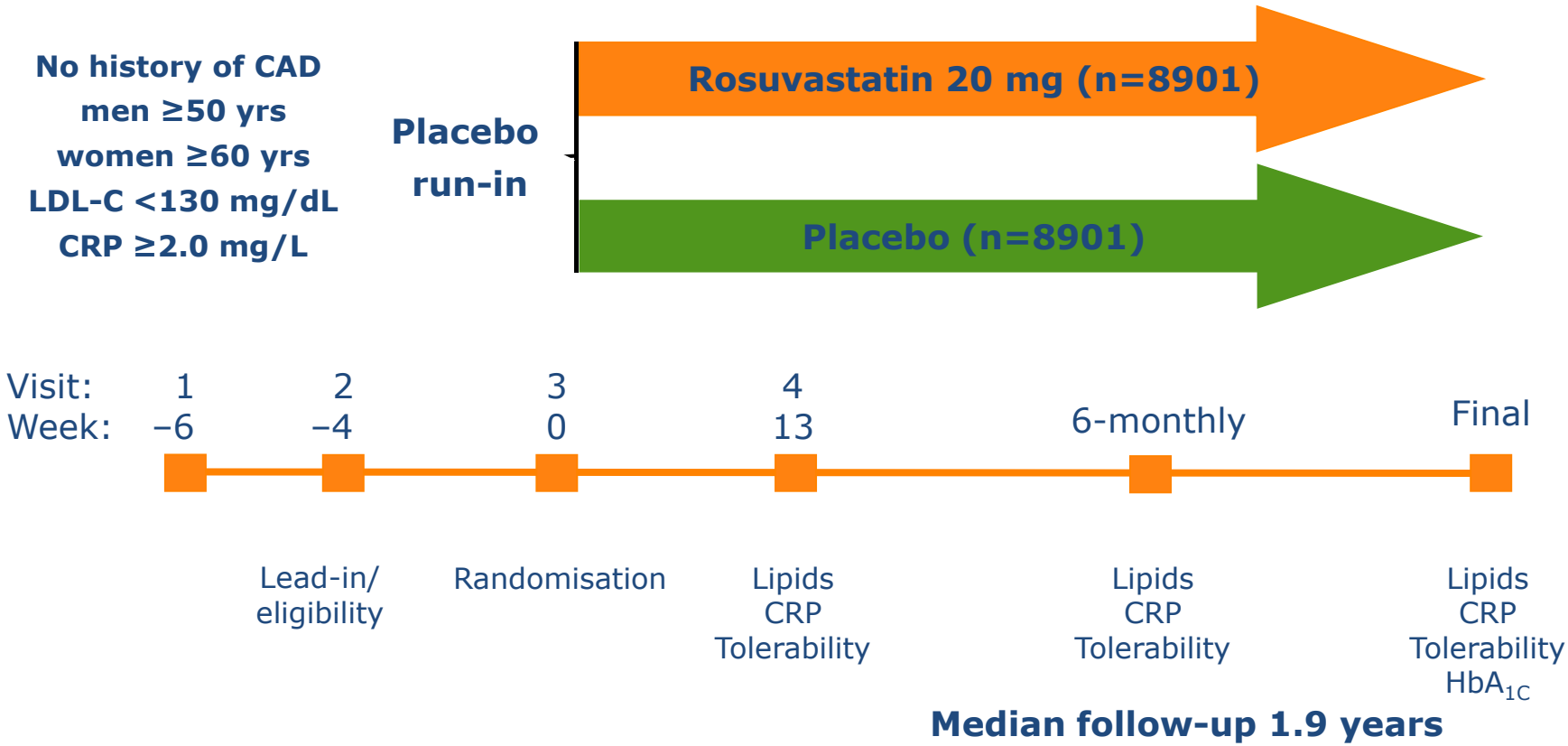
  - pleiotrophic effects of statins work.

  - early intensive statin treatment may show more benefit.

Pleiotropic effects of statins work in ordinary people, too !

Lessons from JUPITER trial

JUPITER – statin as an anti-inflammatory drug ?



CAD=coronary artery disease; LDL-C=low-density lipoprotein cholesterol; CRP=C-reactive protein; HbA_{1c}=glycated haemoglobin

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Baseline characteristics*

	Rosuvastatin n=8901	Placebo n=8901
Age (years)	66 (60-71)	66 (60-71)
Male sex (%)	61.5	62.1
Race (%)		
White	71.4	71.1
Black	12.4	12.6
Hispanic	12.6	12.8
Other	3.6	3.5
BMI (kg/m^2)	28.3 (25.3-32.0)	28.4 (25.3-32.0)
Systolic BP (mmHg)	134 (124-145)	134 (124-145)
Diastolic BP (mmHg)	80 (75-87)	80 (75-87)

*All values are median (interquartile range) or N (%).

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Baseline laboratory parameters*

	Rosuvastatin n=8901	Placebo n=8901
Total cholesterol (mg/dL)	186 (168-200)	185 (169-199)
LDL cholesterol (mg/dL)	108 (94-119)	108 (94-119)
HDL cholesterol (mg/dL)	49 (40-60)	49 (40-60)
Triglycerides (mg/dL)	118 (85-169)	118 (86-169)
hsCRP (mg/L)	4.2 (2.8-7.1)	4.3 (2.8-7.2)
Glucose (mg/dL)	94 (87-102)	94 (88-102)
HbA_{1c}(%)	5.7 (5.4-5.9)	5.7 (5.5-5.9)
Glomerular filtration rate, (ml/min/1.73m^2)	73.3 (64.6-83.7)	73.6 (64.6-84.1)

For hsCRP, values are the average of the values obtained at two screening and visits

*All values are median (interquartile range) or N (%).

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Medical History

Medical History	Rosuvastatin n=8901	Placebo n=8901
Current smoker (%)	15.7	16.0
Family history CHD† (%)	11.2	11.8
Metabolic syndrome‡ (%)	41.0	41.8
Aspirin use (%)	16.6	16.6

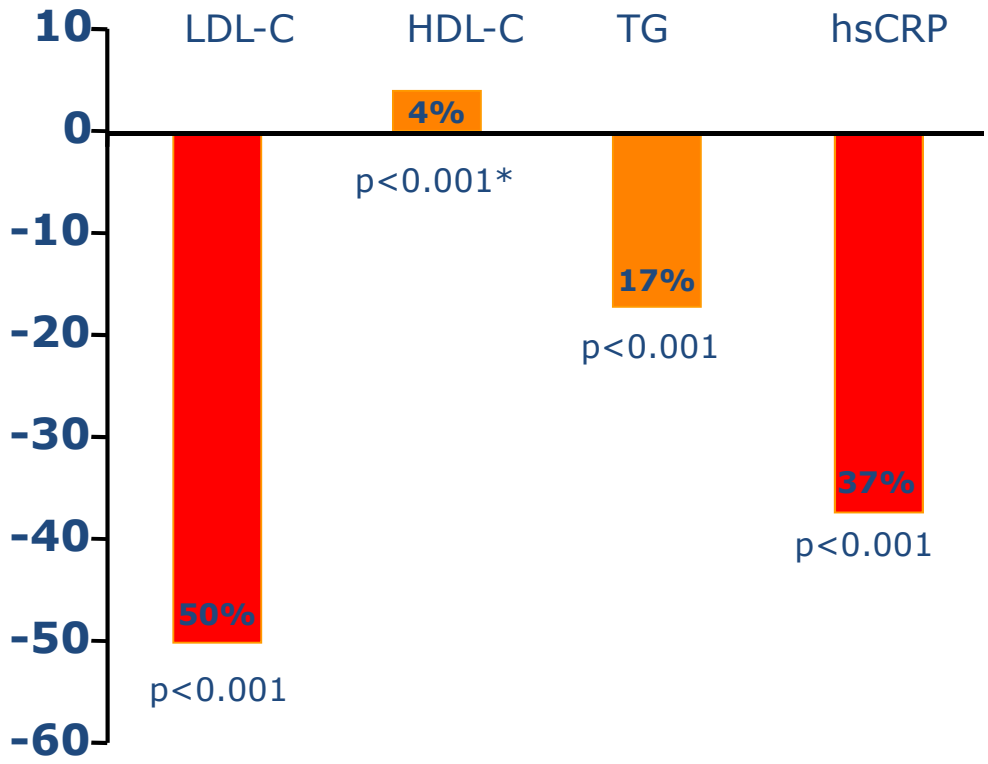
†Family history of premature CHD defined as first degree relative with CHD at age < 55 yrs (male), < 65 yrs (female); ‡ Metabolic syndrome defined according to consensus criteria of AHA/NHLBI

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER

Effects on LDL-C, HDL-C, TG and hsCRP at 12 months;

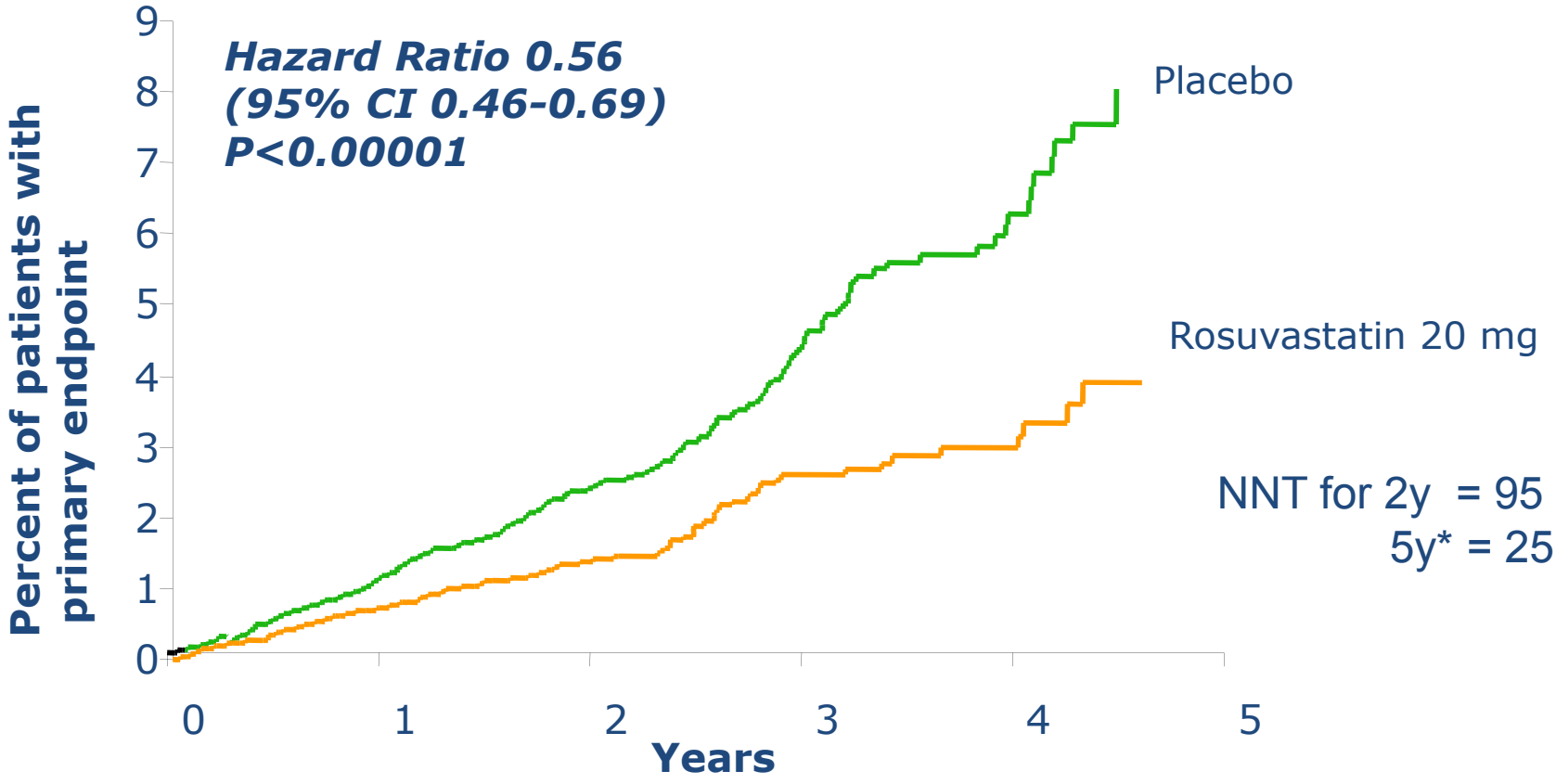
Percentage change between rosuvastatin and placebo



Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Primary Endpoint

Time to first occurrence of a CV death, non-fatal stroke, non-fatal MI, unstable angina or arterial revascularization



Number at risk

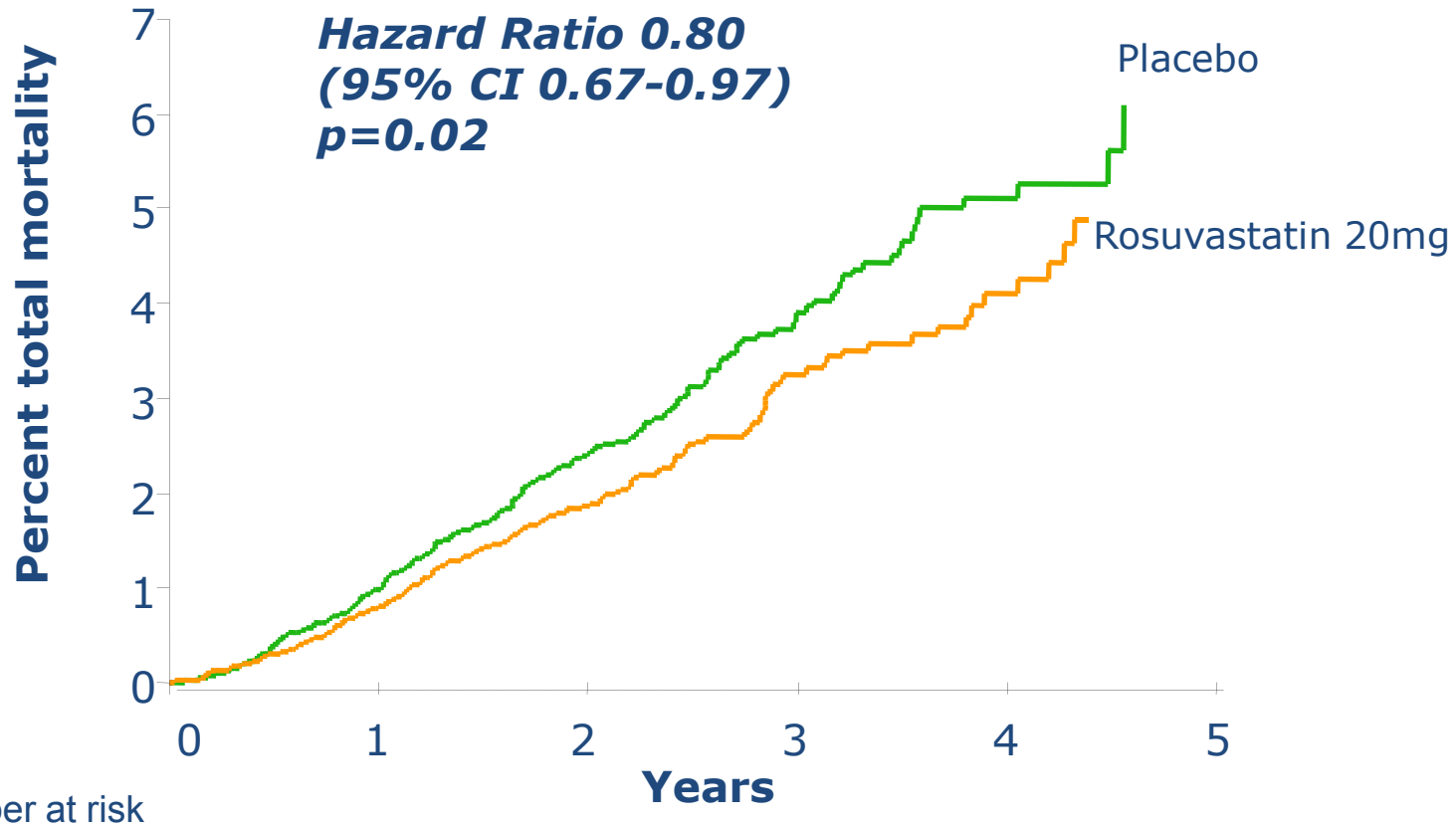
RSV	8901	8412	3893	1353	538	157
Placebo	8901	8353	3872	1333	531	174

*Extrapolated figure based on Altman and Andersen method

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Total Mortality

Death from any cause



Number at risk

RSV	8901	8787	4312	1602	676	227
Placebo	8901	8775	4319	1614	681	246

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER - Primary Endpoint Components

	Placebo [n=8901] n (rate**)	Rosuvastatin [n=8901] n (rate**)	HR	95% CI	p-value
Primary Endpoint (Time to first occurrence of *CV death, MI, stroke, unstable angina, arterial revascularisation*)	**251** (1.36)	**142** (0.77)	**0.56**	0.46-0.69	**<0.001***
Non-fatal MI	**62** (0.33)	**22** (0.12)	**0.35**	0.22-0.58	**<0.001***
Fatal or non-fatal MI	**68** (0.37)	**31** (0.17)	**0.46**	0.30-0.70	**0.0002**
Non-fatal stroke	**58** (0.31)	**30** (0.16)	**0.52**	0.33-0.80	**0.003**
Fatal or non-fatal stroke	**64** (0.34)	**33** (0.18)	**0.52**	0.34-0.79	**0.002**
Arterial Revascularization	**131** (0.71)	**71** (0.38)	**0.54**	0.41-0.72	**<0.0001**
Unstable angina†	**27** (0.14)	**16** (0.09)	**0.59**	0.32-1.10	**0.09**
CV death, stroke, MI	**157** (0.85)	**83** (0.45)	**0.53**	0.40-0.69	**<0.001***
Revascularization or unstable angina	**143** (0.77)	**76** (0.41)	**0.53**	0.40-0.70	**<0.001***

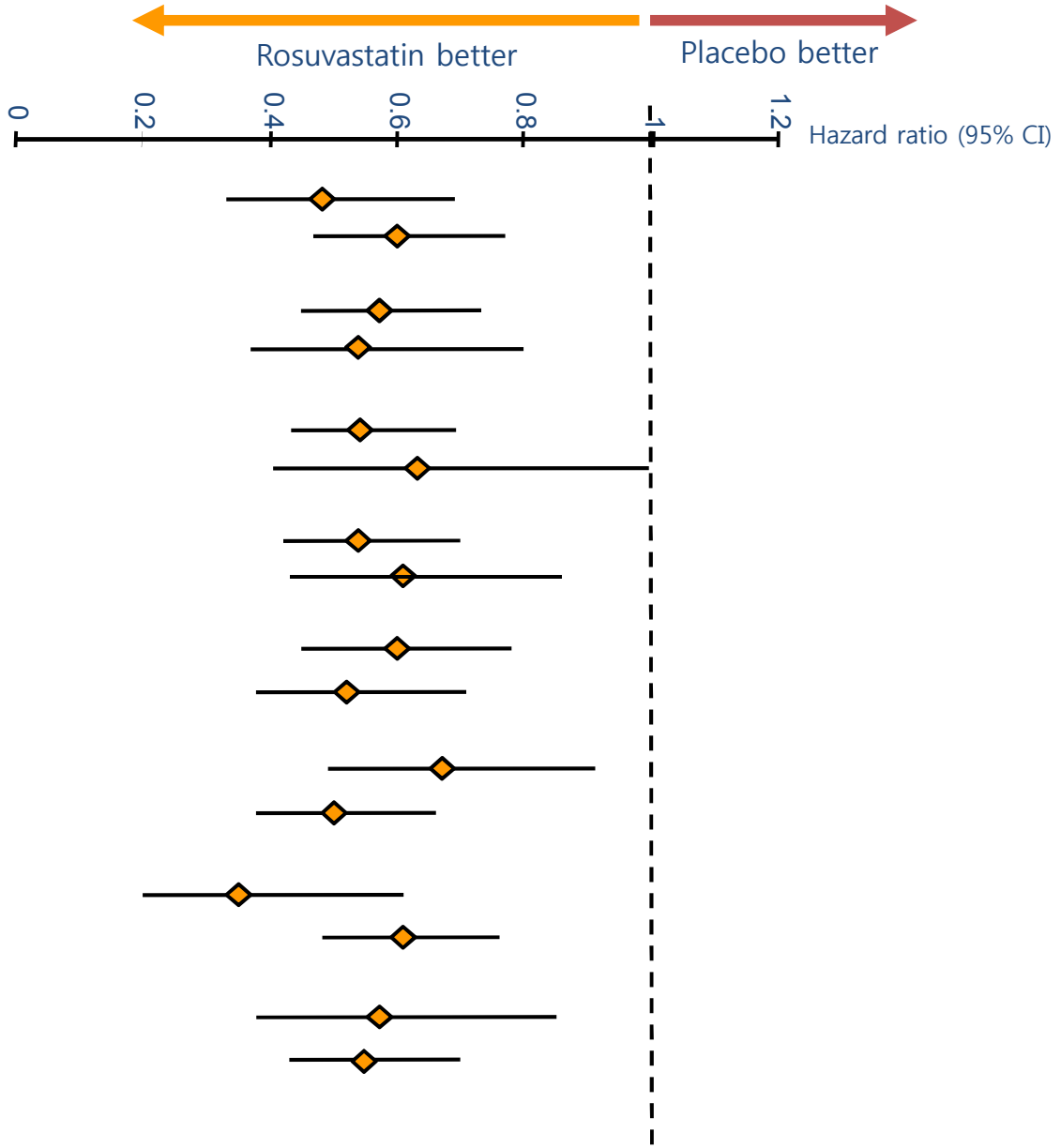
** Rates are per 100 person years; † Hospitalisation due to unstable angina; *Actual p-value was < 0.00001

HR – Hazard Ratio; CI – Confidence Limit

Ridker P *et al*. *N Eng J Med* 2008;**359**: 2195-2207

JUPITER – Subgroup analysis

	N	P- value*
Age		0.32
≤ 65 years	8,541	
>65 yrs	9,261	
Gender		0.80
Males	11,001	
Females	6,801	
Race		0.57
White	12,683	
Non-white	5,117	
Hypertension		0.53
Yes	10,208	
No	7,586	
Region		0.51
US or Canada	6,041	
Other	11,761	
Metabolic syndrome		0.14
Yes	7,375	
No	10,296	
Family history of CHD		0.07
Yes	2,045	
No	15,684	
Framingham risk score		0.99
≤10%	8,882	
>10%	8,895	



Ridker P *et al. N Eng J Med* 2008;**359**: 2195-2207

JUPITER

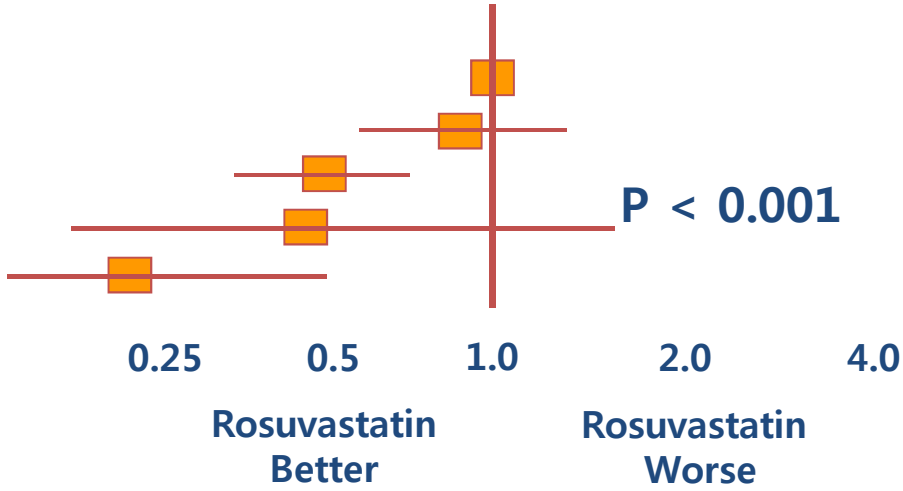
LDL reduction, hsCRP reduction, or both?

	N	Rate
Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥2 mg/L	1384	1.11
LDL<70mg/dL,hsCRP≥2 mg/L	2921	0.62
LDL≥70mg/dL,hsCRP<2 mg/L	726	0.54
LDL<70mg/dL,hsCRP<2 mg/L	2685	0.38

P < 0.001

Placebo	7832	1.11
LDL≥70mg/dL,hsCRP≥1 mg/L	1874	0.95
LDL<70mg/dL,hsCRP≥1 mg/L	4662	0.56
LDL≥70mg/dL,hsCRP<1 mg/L	236	0.64
LDL<70mg/dL,hsCRP<1 mg/L	944	0.24

P < 0.001

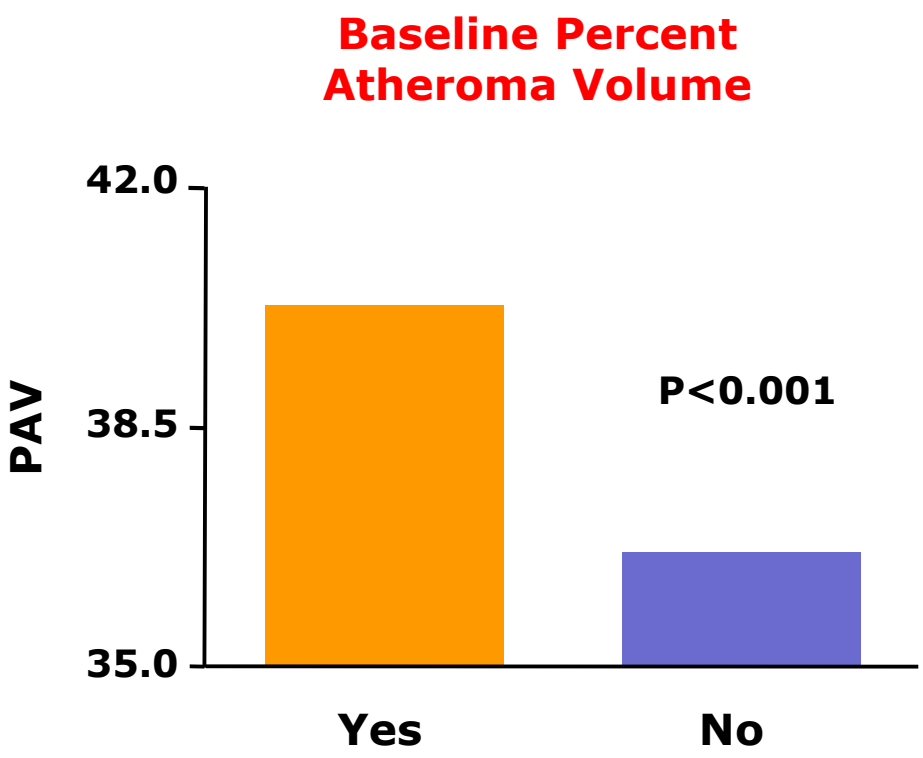


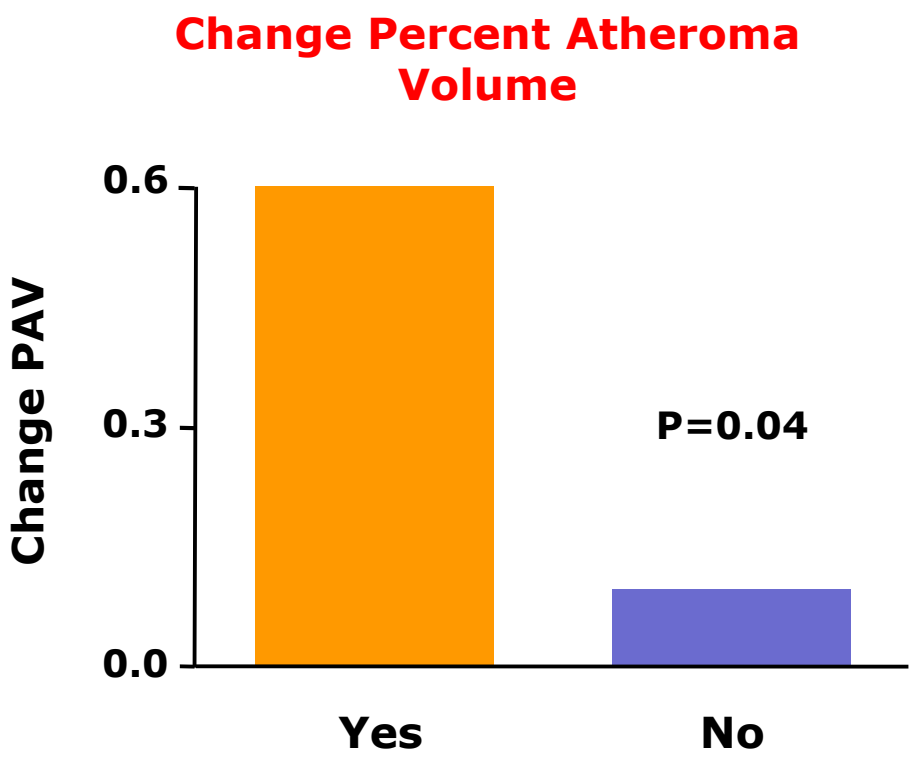
Can statins reverse atherogenesis ?

Atheroma Burden and Incident Clinical Events

ILLUSTRATE (N=1180)

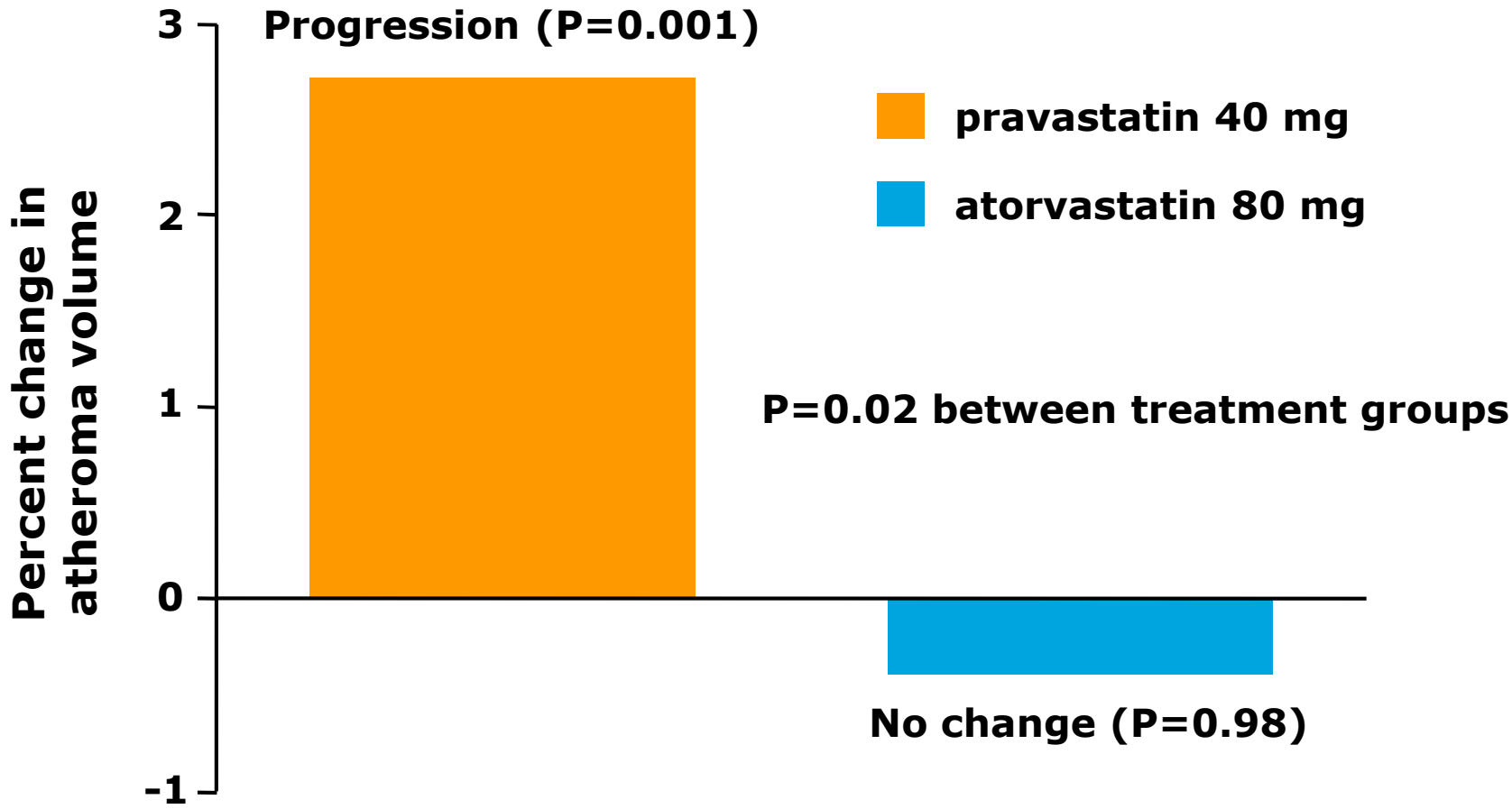
Incidence of cardiovascular death, myocardial infarction, hospitalisation for unstable angina, stroke and coronary revascularisation





Nicholls S. AHA Scientific Sessions 2007

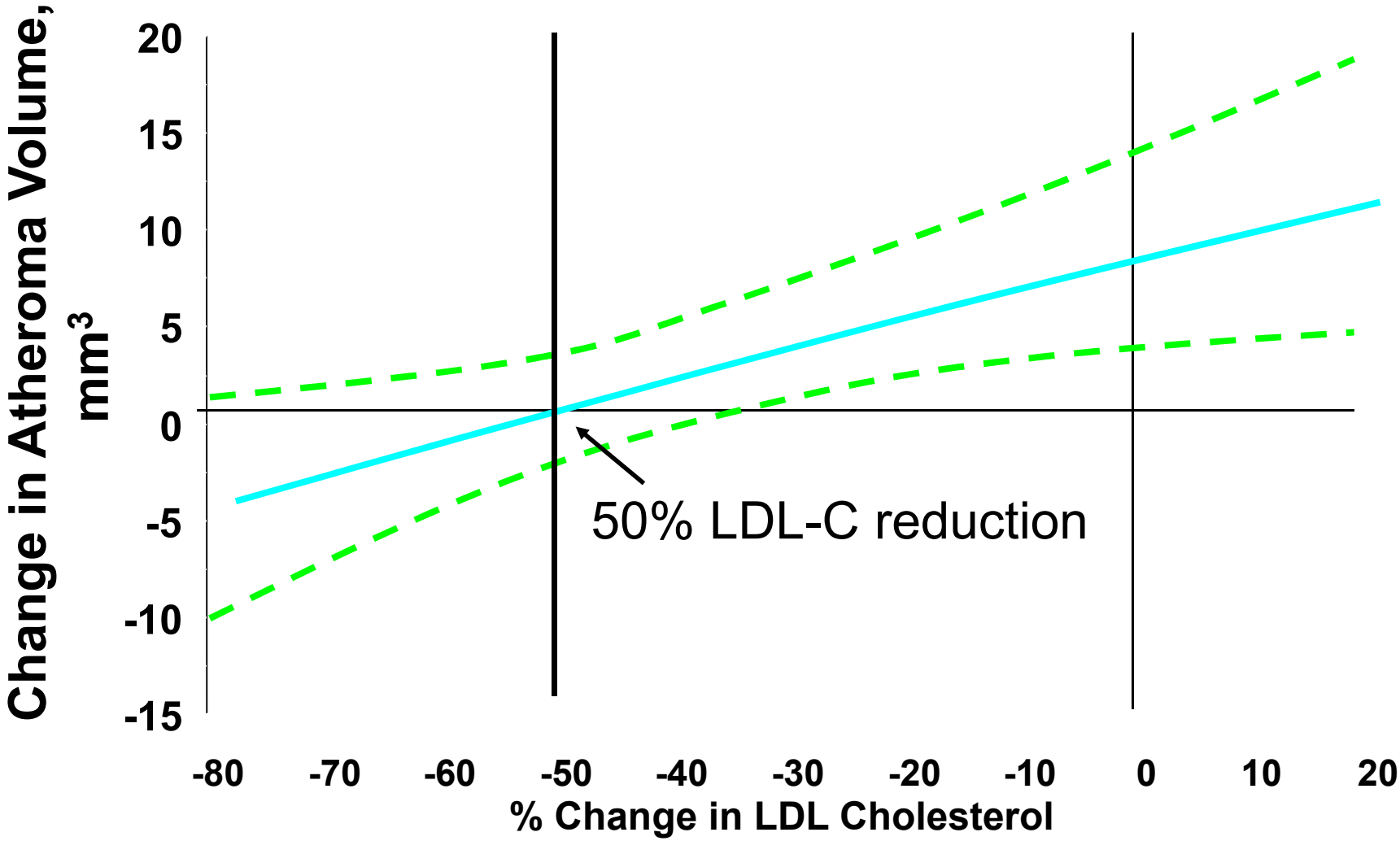
REVERSAL: Benefit of Intensive LDL-C Lowering on Plaque Progression



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

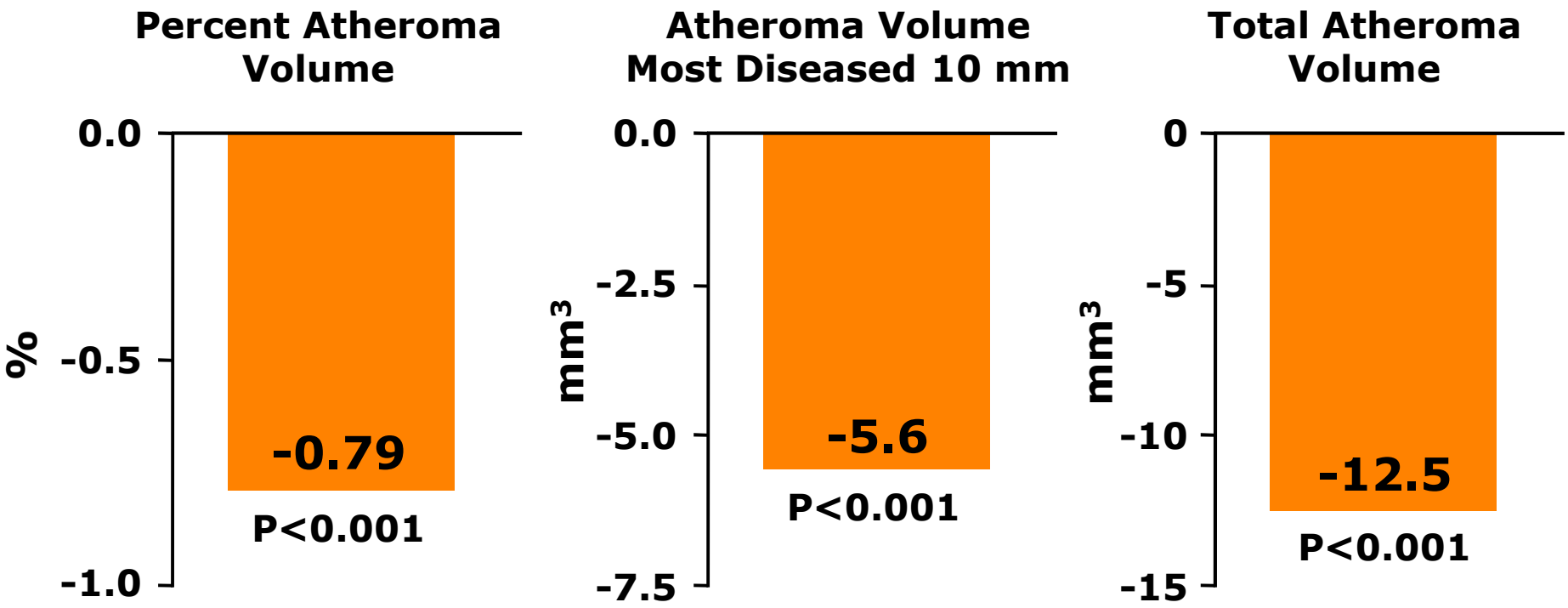
REVERSAL

50% LDL Cholesterol Reduction stops atheroma growth



ASTEROID:
Atheroma regression with Statin Therapy

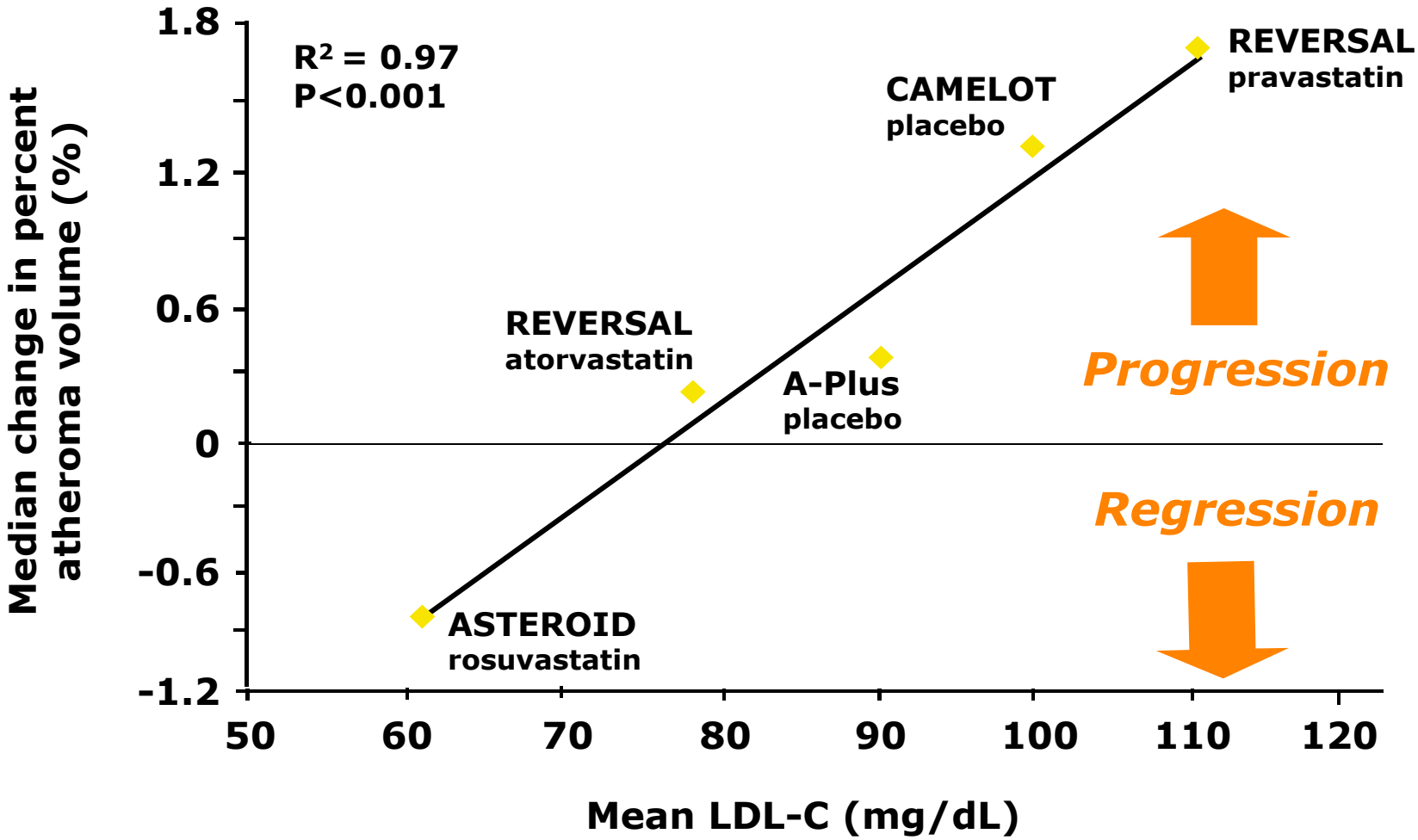
349 patients treated with rosuvastatin 40 mg for 24 months
LDL-C 60.8 mg/dL and increase HDL-C by 14.7%



Nissen SE, Nicholls S et al. JAMA 2006;295:1555–1565

ASTEROID

60% LDL Cholesterol Reduction or 60 mg/dl LDLc reverses atheroma growth

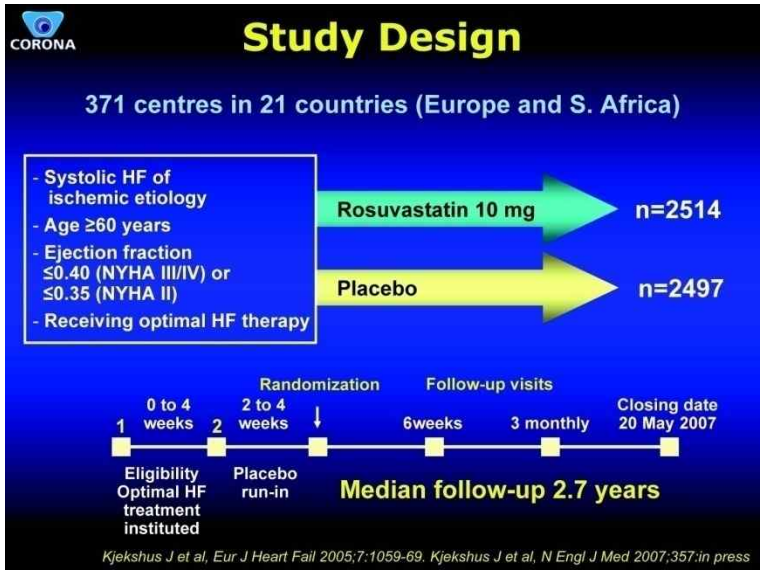


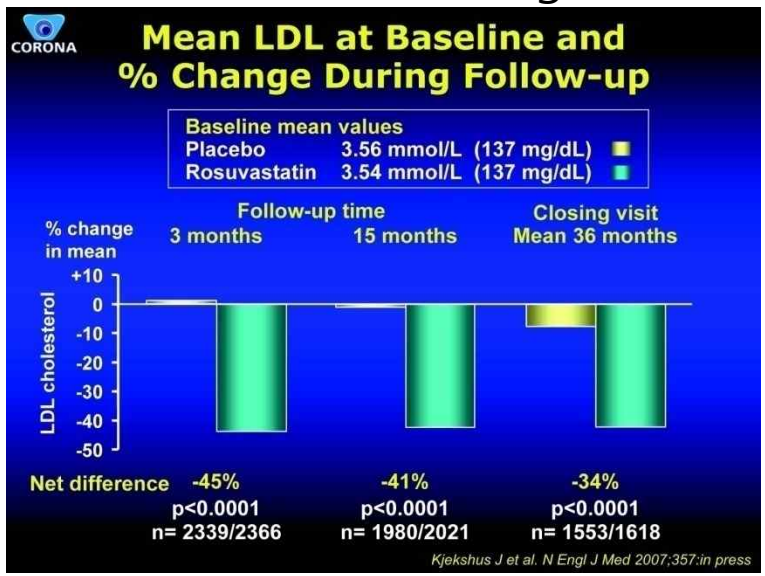
Nissen S et al. JAMA 2006

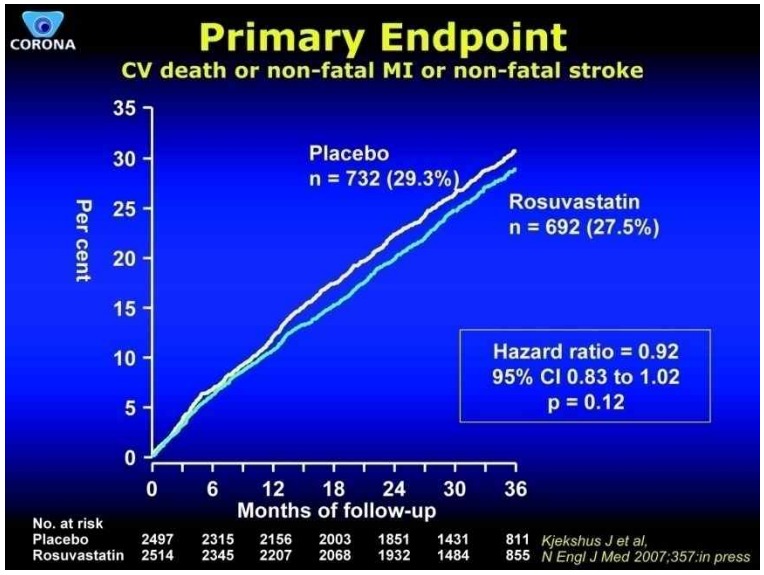
Statin failure

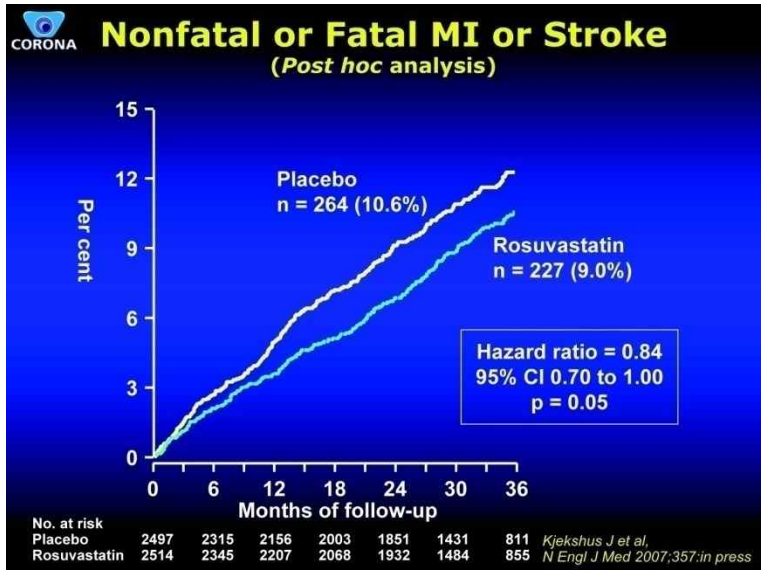
Statins in HF
CORONA

LDLc ; - 44% (from 137 to 76mg/dl)
TG ; from 178 to 138 mg/dl
HDLc ; from 48 to 50 mg/dl
CRP ; from 3.1 to 2.1 mg/L



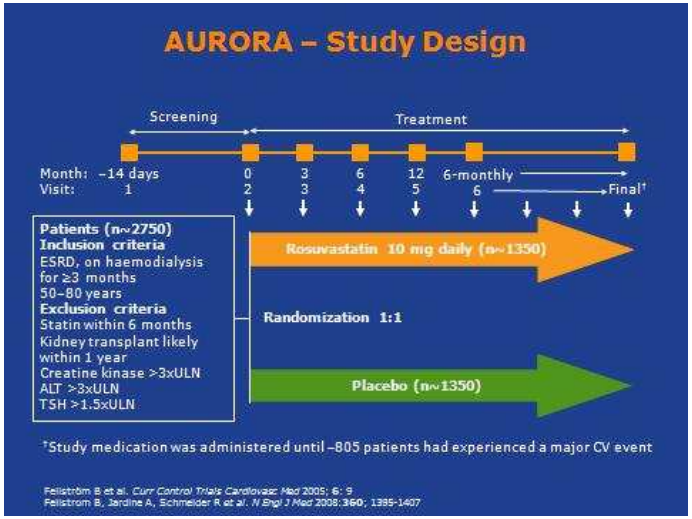


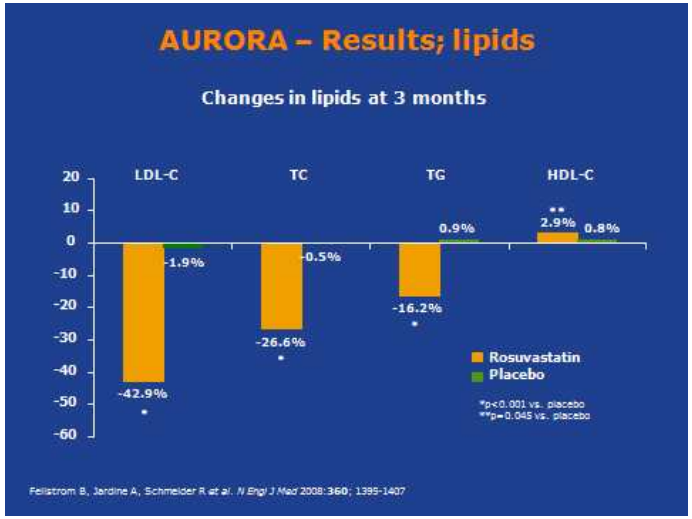


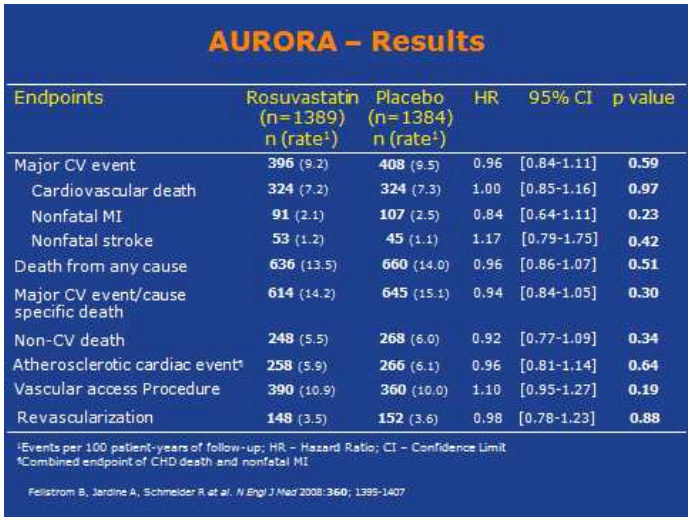


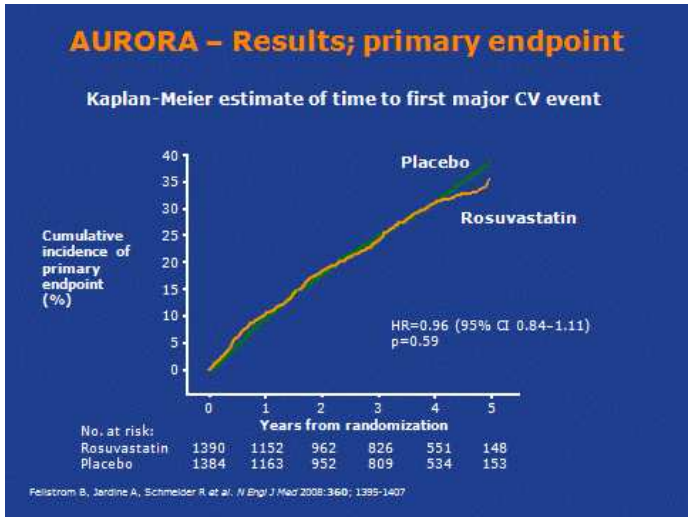
Statins in ESRD
AURORA

LDLc ; 100mg/dl
TG ; 156 mg/dl
HDLc ; 45 mg/dl
CRP ; 5.0 mg/L



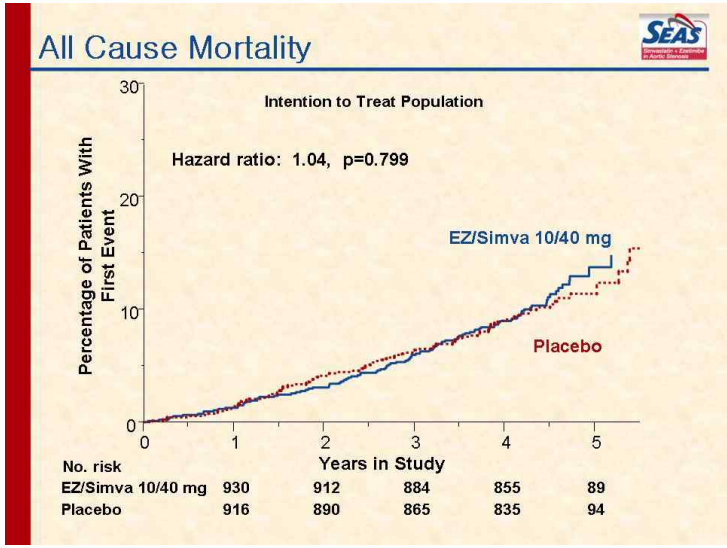


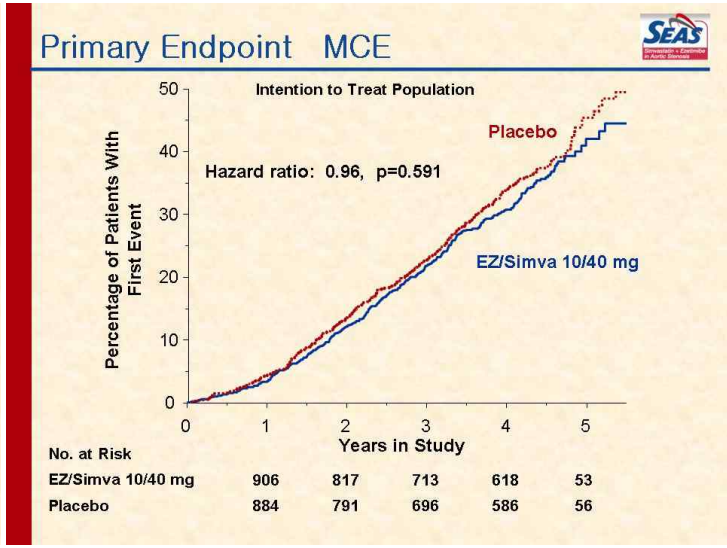


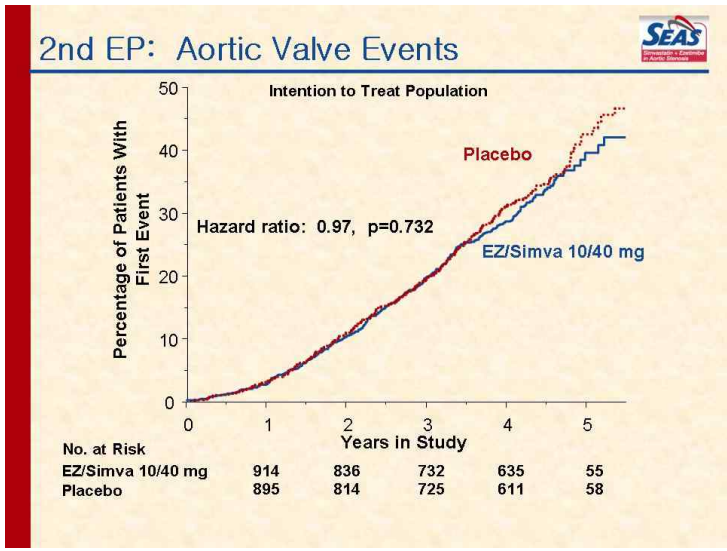


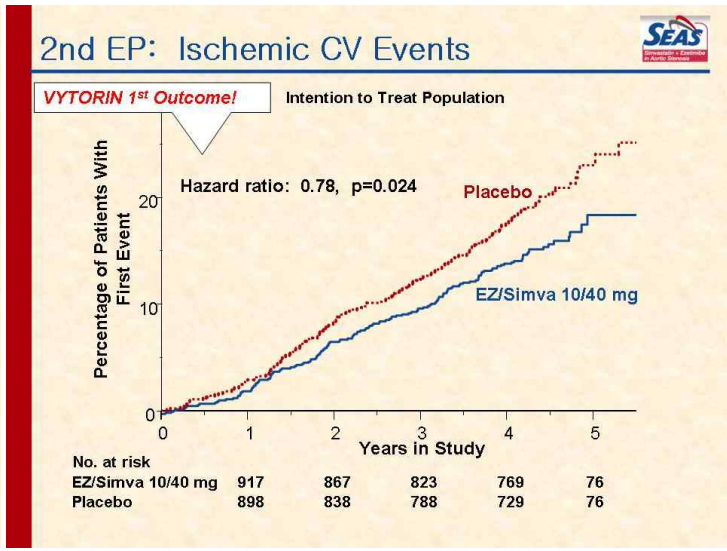
Statins in AS
SEAS

LDLc ; 139 vs. 53 mg/dl (simva/ez 40/10)

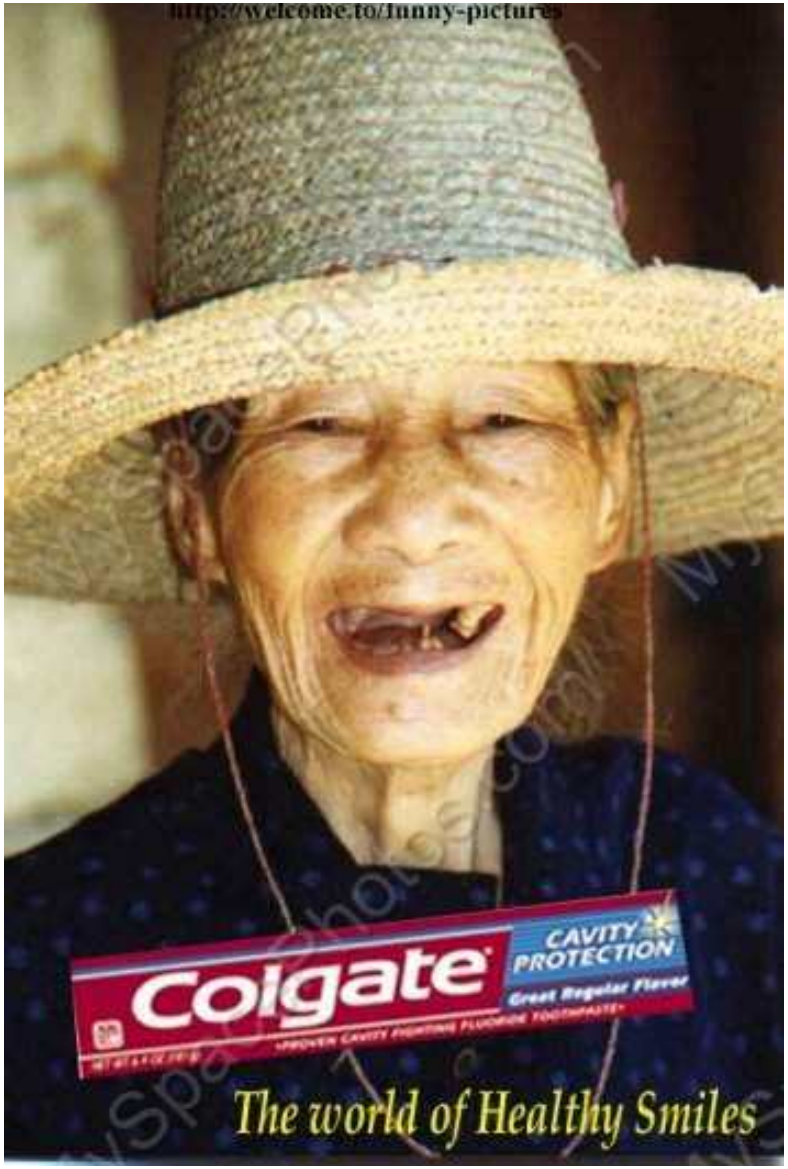




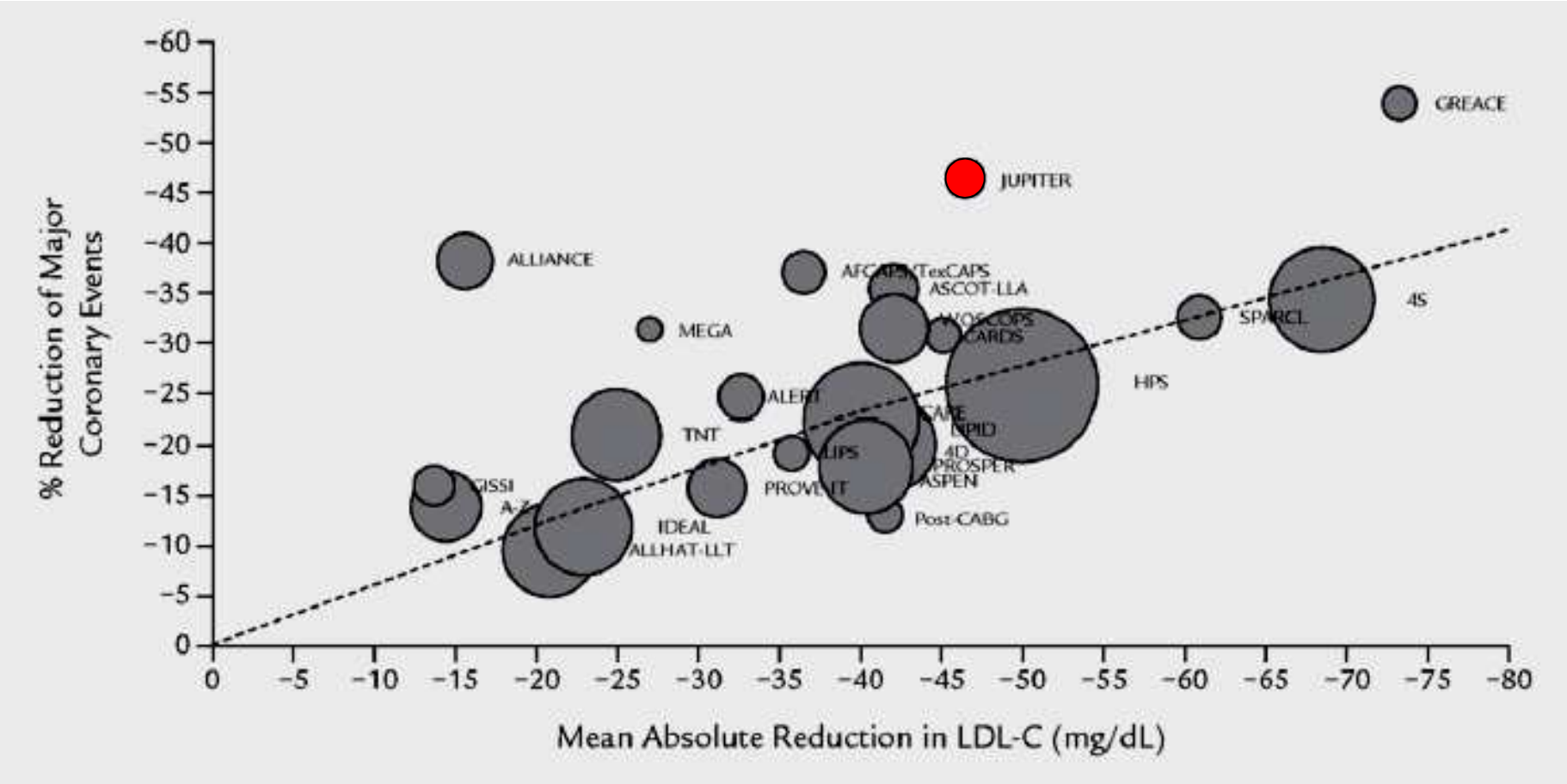




It was just TOO late !



Statin Myth Continues



Clin Ther. 2009;31:236-244

Summary

- Appropriate intervention helps esp. for the patients with ACS and unstable angina, and multi-vessel disease.
- Early and aggressive statin treatment should be implemented to reduce inflammation as well as LDL cholesterol in acute stage to stabilize atheroma.
- Intensive statin treatment can reverse atherogenesis.
- Earlier statin management can maximize statin effect as proven by JUPITER trial.