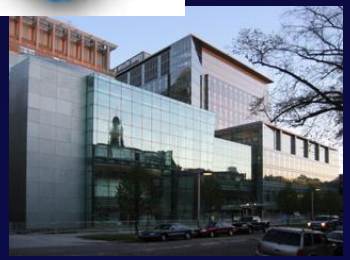
Clinical Benefits of Statin Therapy: LDL-lowering and/or Anti-Inflammatory?

Peter Libby

Brigham & Women's Hospital

Harvard Medical School



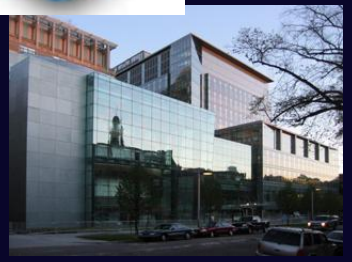
Cardiology Update

Davos, CH February 2013

Peter Libby

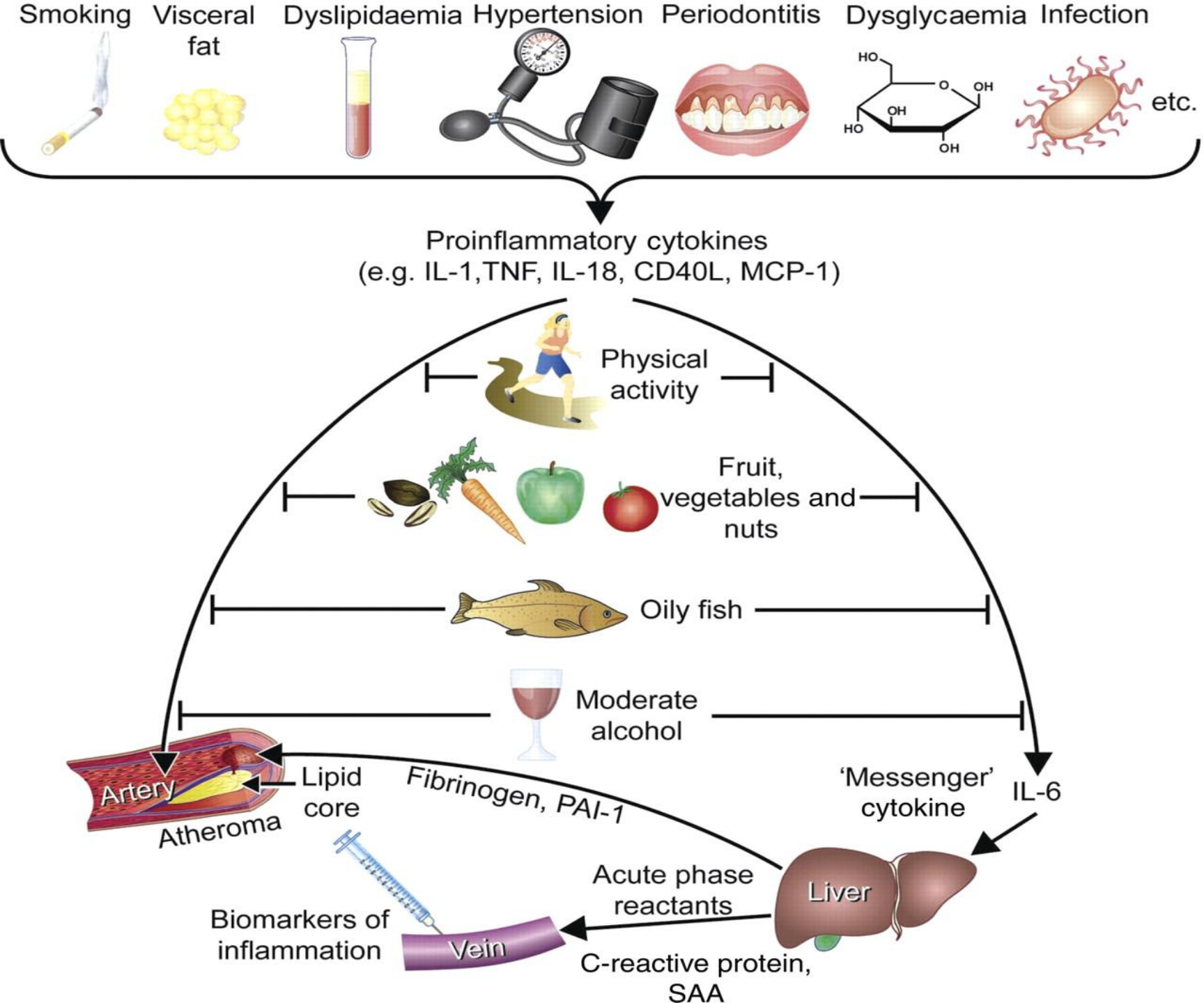
Brigham & Women's Hospital
Harvard Medical School

Dr. Libby does not accept payments from Pharma. He serves as an unpaid consultant and contributes to clinical trials sponsored by Pharma. BWH has patents concerning the use of CRP in CVD.



Clinical Benefits of Statin Therapy: LDL-lowering and/or Anti-Inflammatory?

YES

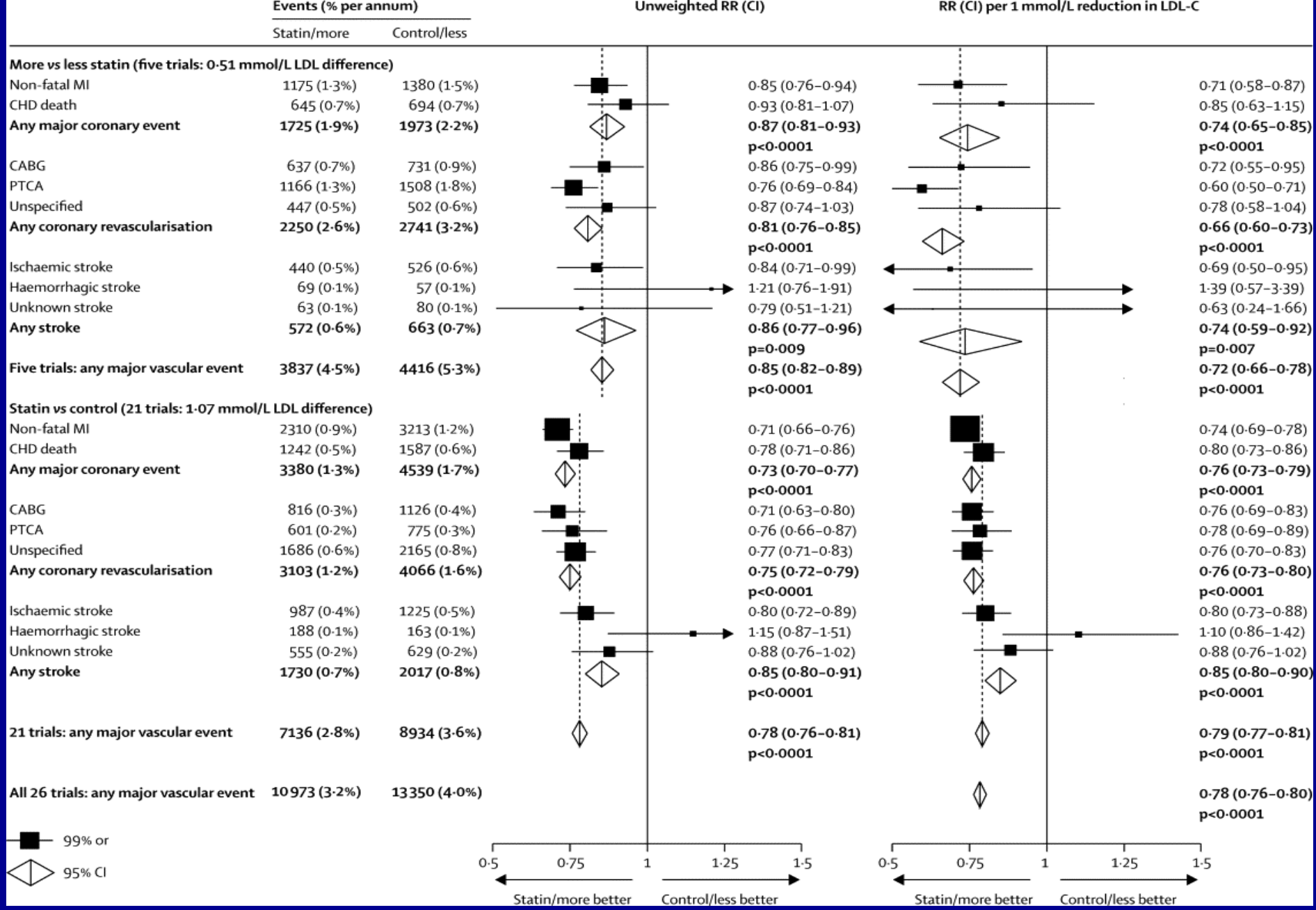


Lifestyle a key to CV prevention

Libby & Crea

European Heart Journal 2010

European Heart Journal



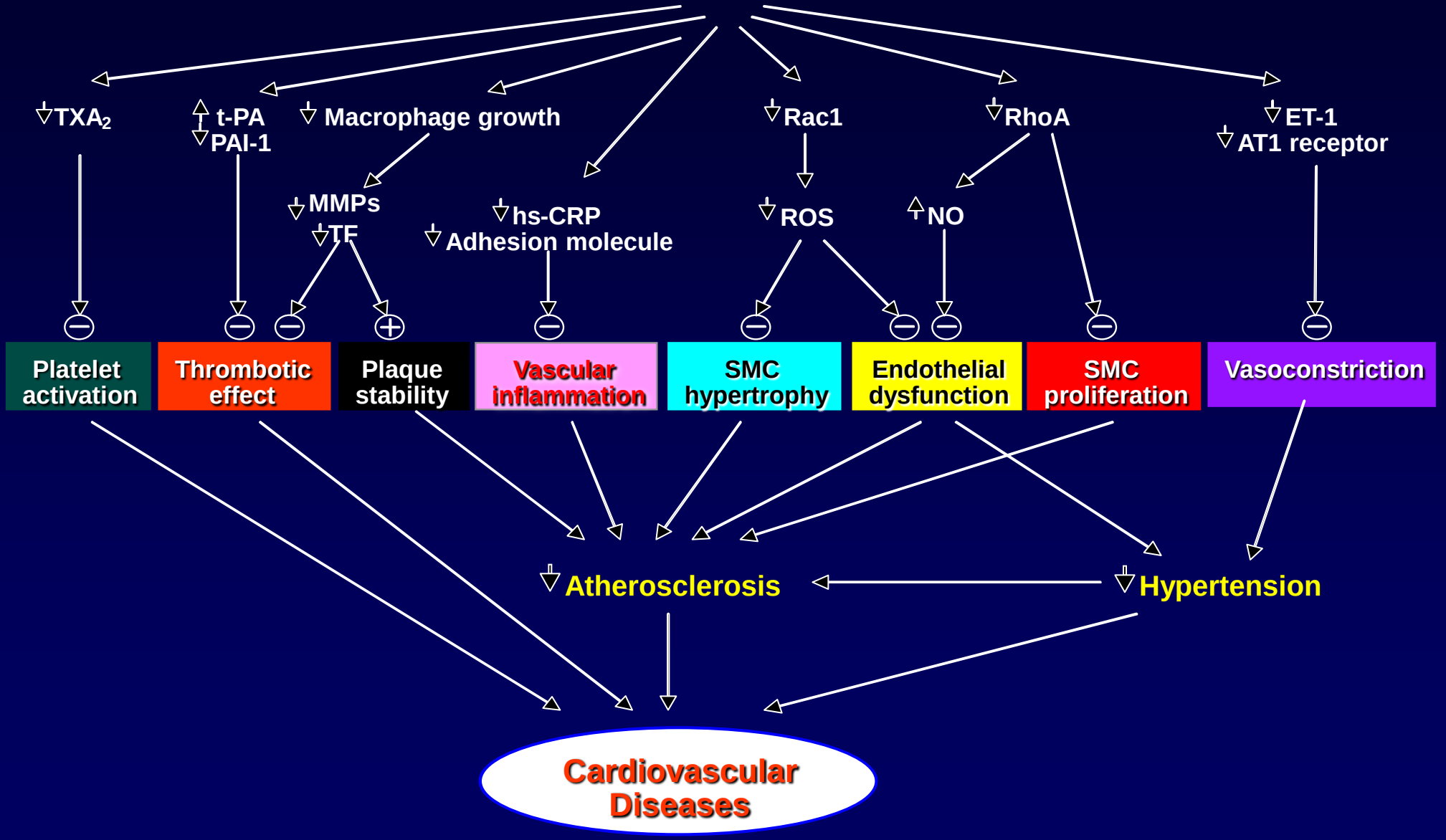
Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. *Lancet. 2010;376:1670-1681.*

Mechanisms of Reduction of Cardiovascular Events by Statin Therapy?

- LDL-Lowering effect
- "Pleiotropic" effects

Libby P, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. Nature Medicine 2002;8:1257-1262.

Putative Pleiotropic Effects of Statins



Takemoto & Liao. *Arterioscl. Thromb. Vasc. Biol.* 2001

Possible Non-LDL Lowering Effects of Statins Relevant to Atherosclerosis

- Reducing thrombogenicity
- Opposing vasospasm
- Decreasing inflammation
- Stabilizing the fibrous cap

Possible Non-LDL Lowering Effects of Statins Relevant to Atherosclerosis

- Decreased inflammation

Statins Decrease Inflammation in Mouse Atheromata Despite Modest LDL Lowering

1508 Circulation October 3, 2006

Nahrendorf et al.

HCD=high colesterol diet
CNR=contrast/noise ratio (MRI)
TBR=target/background ratio (Near IR)

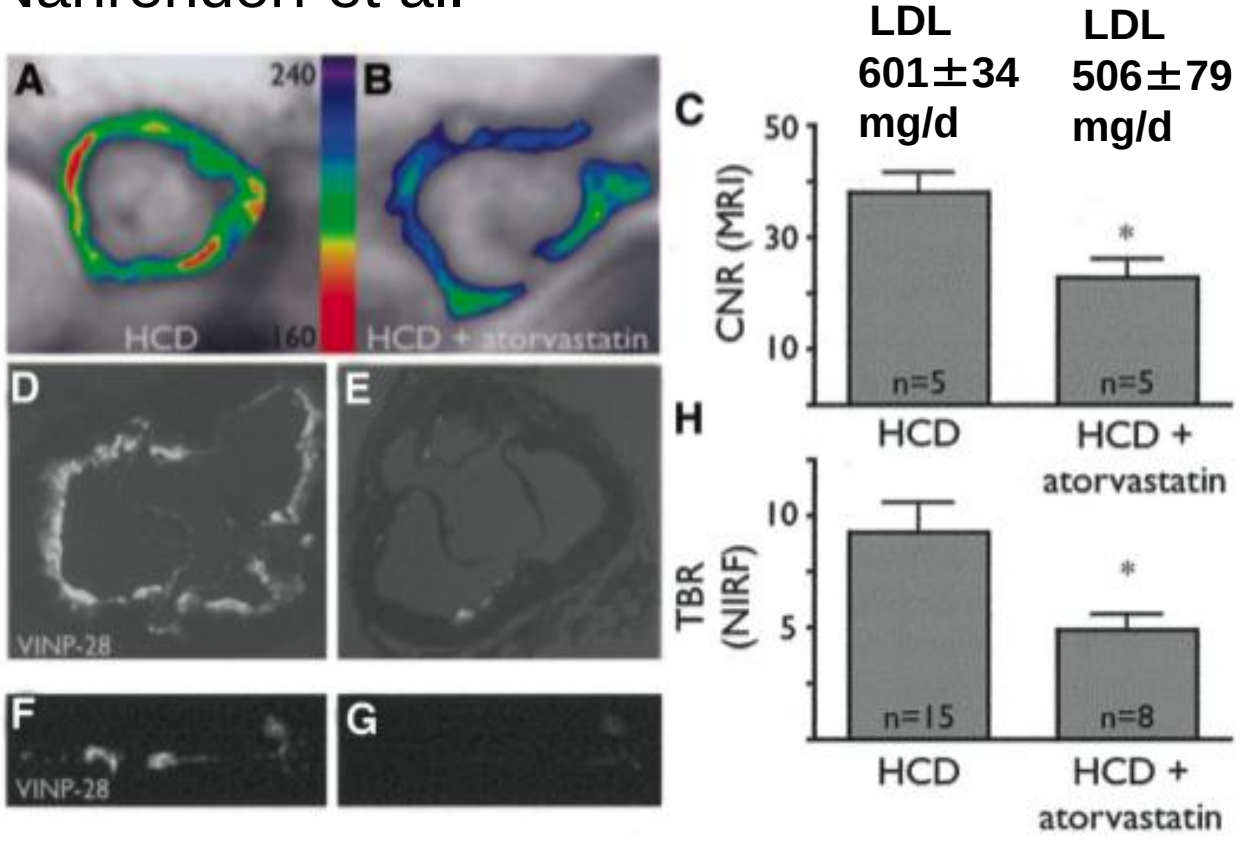


Figure 5. Noninvasive MRI assessment of VCAM-1 expression after atorvastatin administration. A, Short-axis MRI of the aortic root of an untreated apoE$^{-/-}$ mouse on an HCD after VINP-28 injection with color-coded signal intensity. B, MRI of HCD+atorvastatin apoE$^{-/-}$ mouse after VINP-28 injection. An attenuated signal drop in the aortic root wall compared with untreated mouse was noted. The red color encodes high VCAM-1 expression. C, After injection of VINP-28, the MRI contrast-to-noise ratio diminished in atorvastatin-treated mice (mean±SD; *P<0.05 vs HCD). D, E, NIR microscopy of aortic root depicted in A and B. Fluorescent signal originating from VINP-28 comprised the whole-root circumference (D), but less so in atorvastatin-treated mice (E). F, H, Fluorescent reflectance imaging of the excised aorta of an untreated (F) and atorvastatin-treated (G) mouse showed reduced NIR signal in statin-treated mice. The target-to-background ratio was reduced in aortas of treated mice (H; mean±SD; *P<0.05 treated vs untreated mice).

Noninvasive MR Imaging of VCAM-1 Expression: 8 weeks of statin treatment reduced serum cholesterol moderately, as expected, in mice (HCD, 601±34 mg/dL; HCD plus atorvastatin, 506±79 mg/dL; *P<0.05)*

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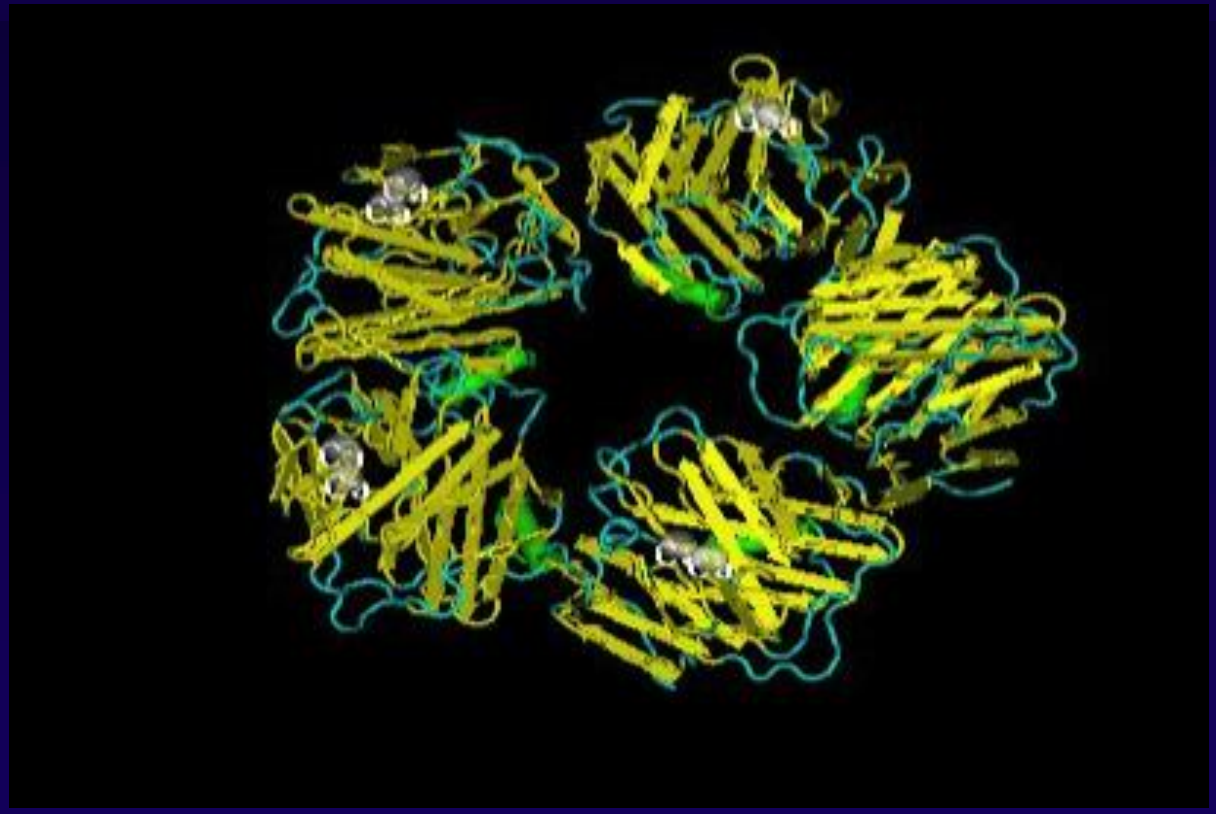
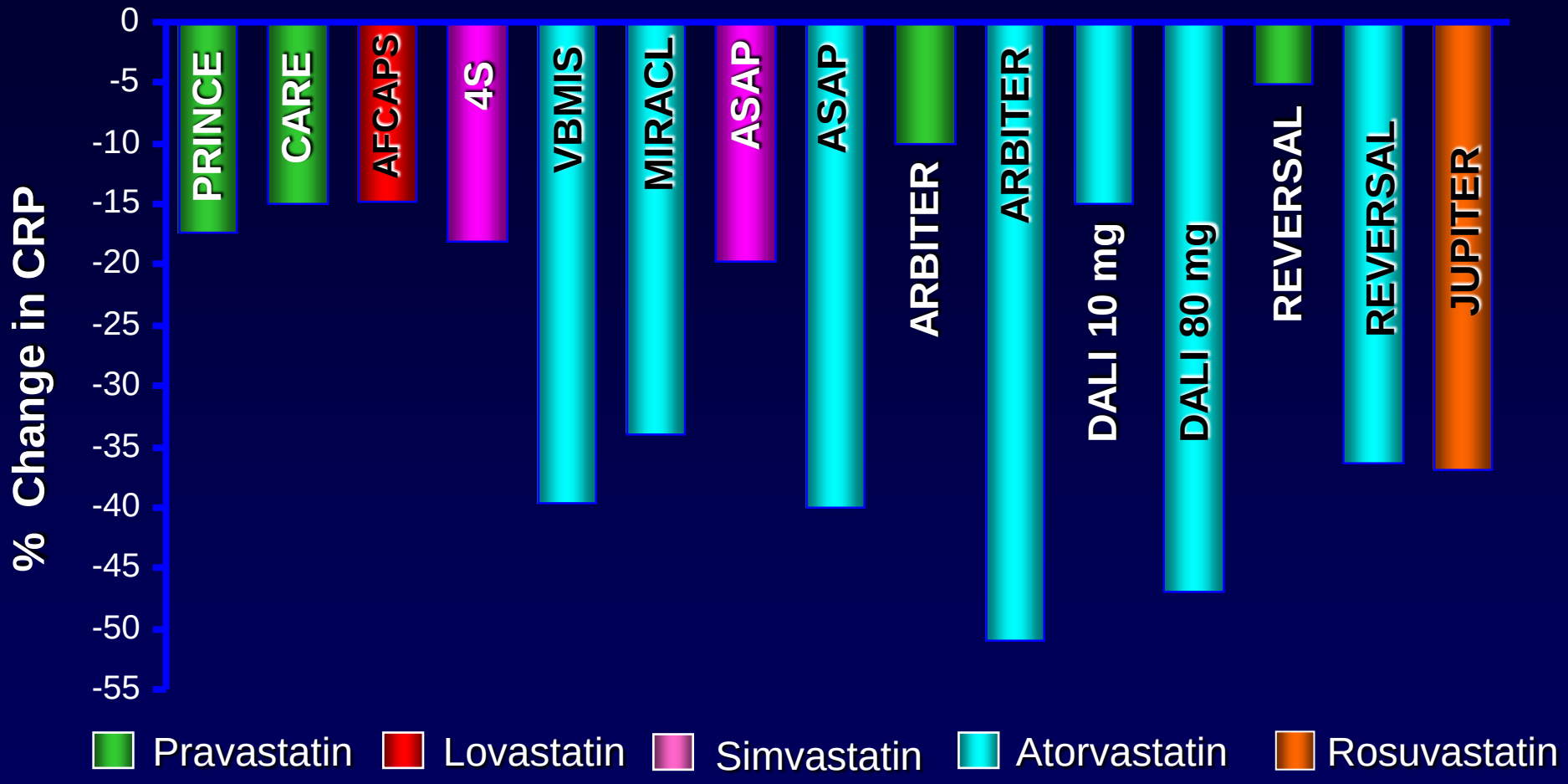
Can we use inflammatory markers in the clinic?



C-reactive protein: CRP

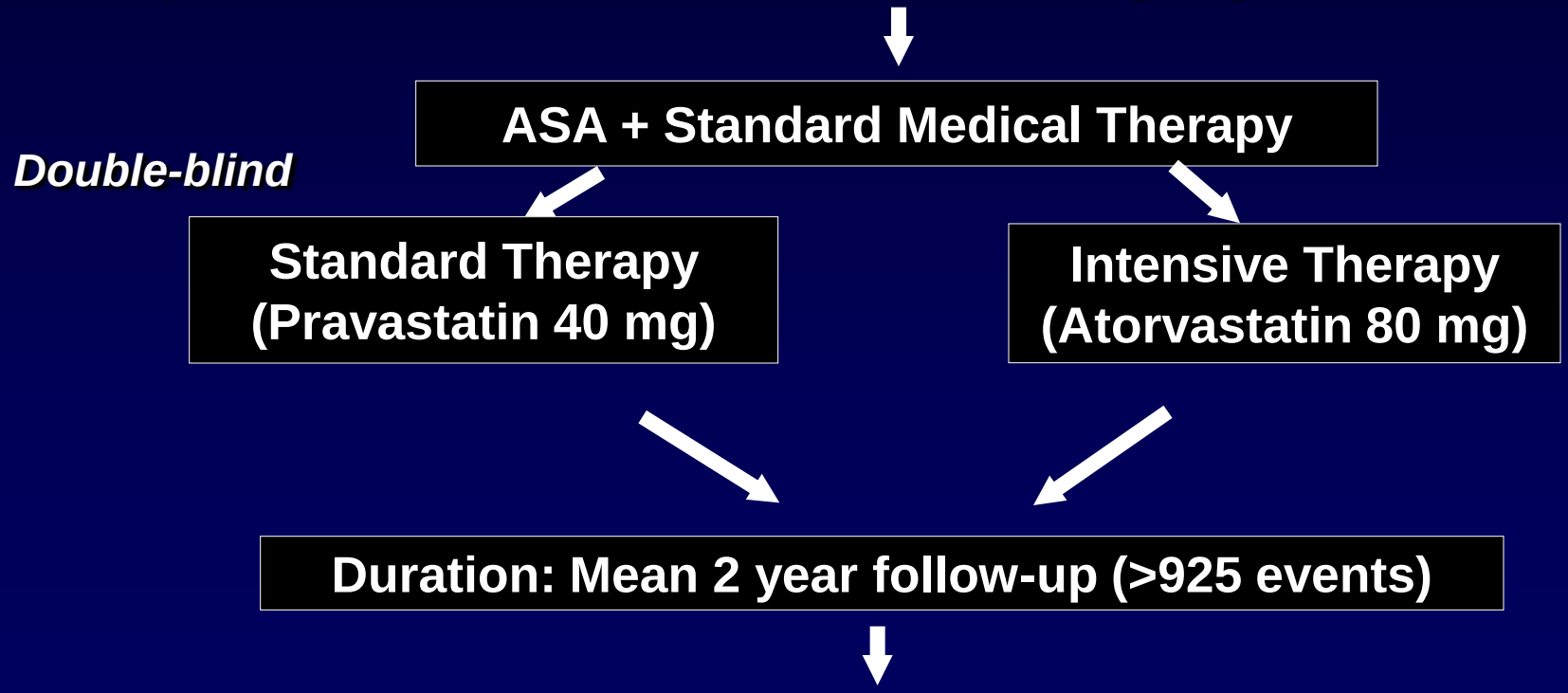
Statin Therapy Reduces C-Reactive Protein



Albert et al. JAMA. 2001;286:64-70; Crea et al. Clin Cardiol. 2002;25:461-466; Kinlay et al. Am J Cardiol. 2002;89:1205-1207; Ridker et al. N Engl J Med. 2001;344:1959-1965; Ridker et al. Circulation. 1998;98:839-844; Taylor et al. Circulation. 2002;106:2055-2060; van de Ree et al. Atherosclerosis. 2003;166:129-135; van Wissen et al. Atherosclerosis. 2002;165:361-366; Nissen et al. JAMA. 2004;291:1071-1080; Ridker et al. NEJM 2008:359:2195-2207.

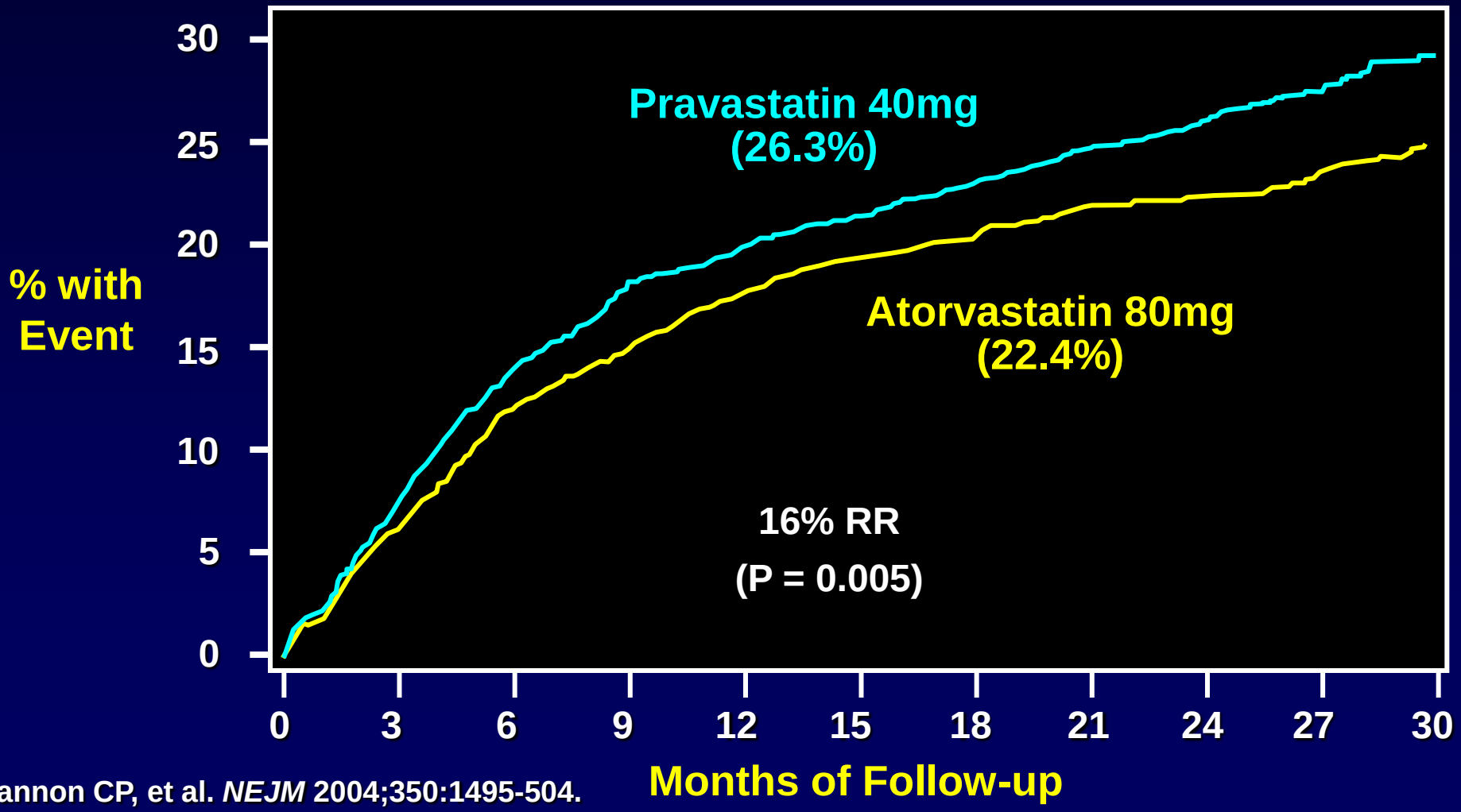
PROVE IT - TIMI 22: Lipid Lowering Study Design

4,162 patients with an Acute Coronary Syndrome < 10 days



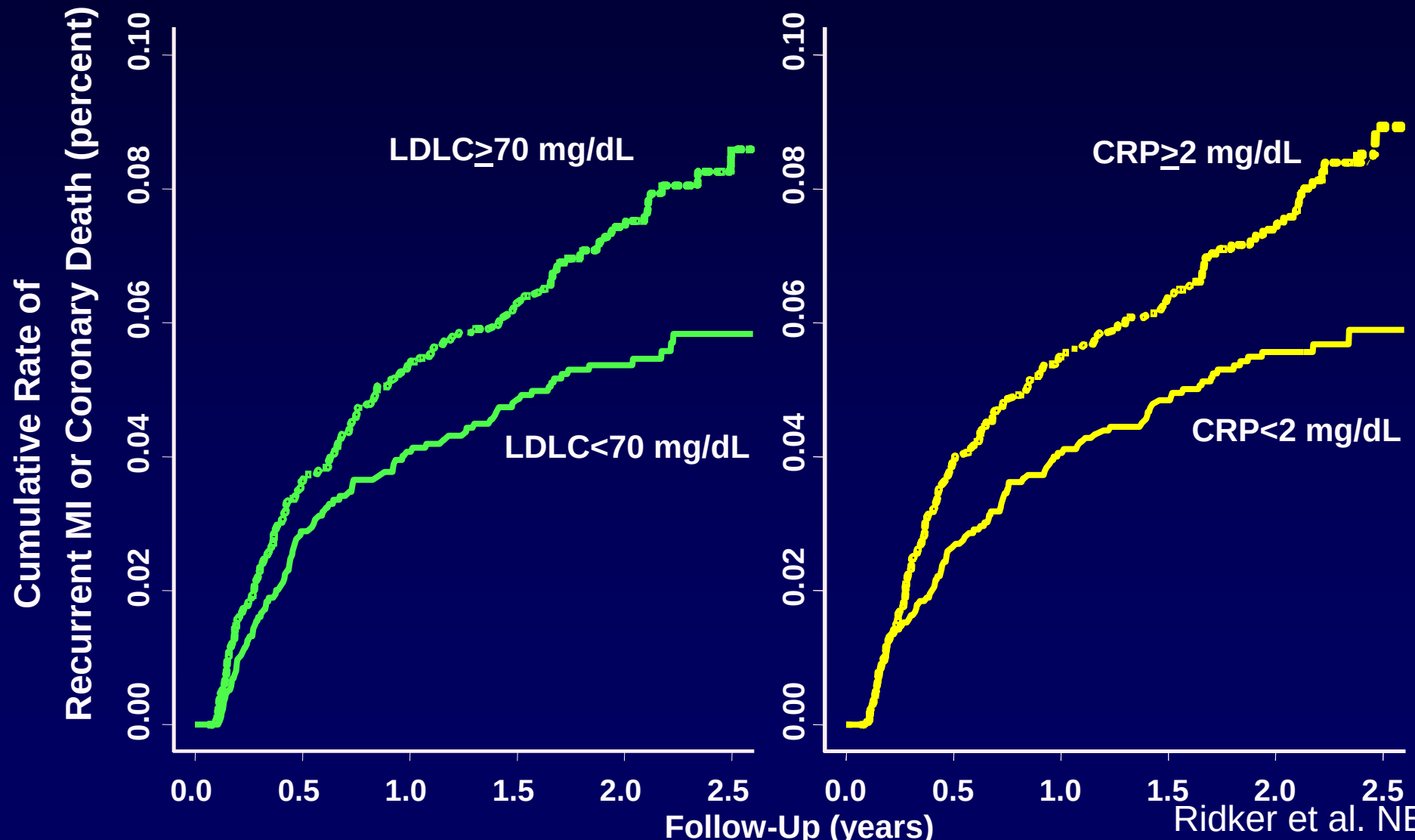
Primary Endpoint: Death, MI, Documented UA requiring hospitalization, revascularization (> 30 days after randomization), or Stroke

All-Cause Death or Major CV Events in All Randomized Subjects



Cannon CP, et al. *NEJM* 2004;350:1495-504.

Clinical Relevance of Achieved LDL and Achieved CRP After Treatment with Statin Therapy



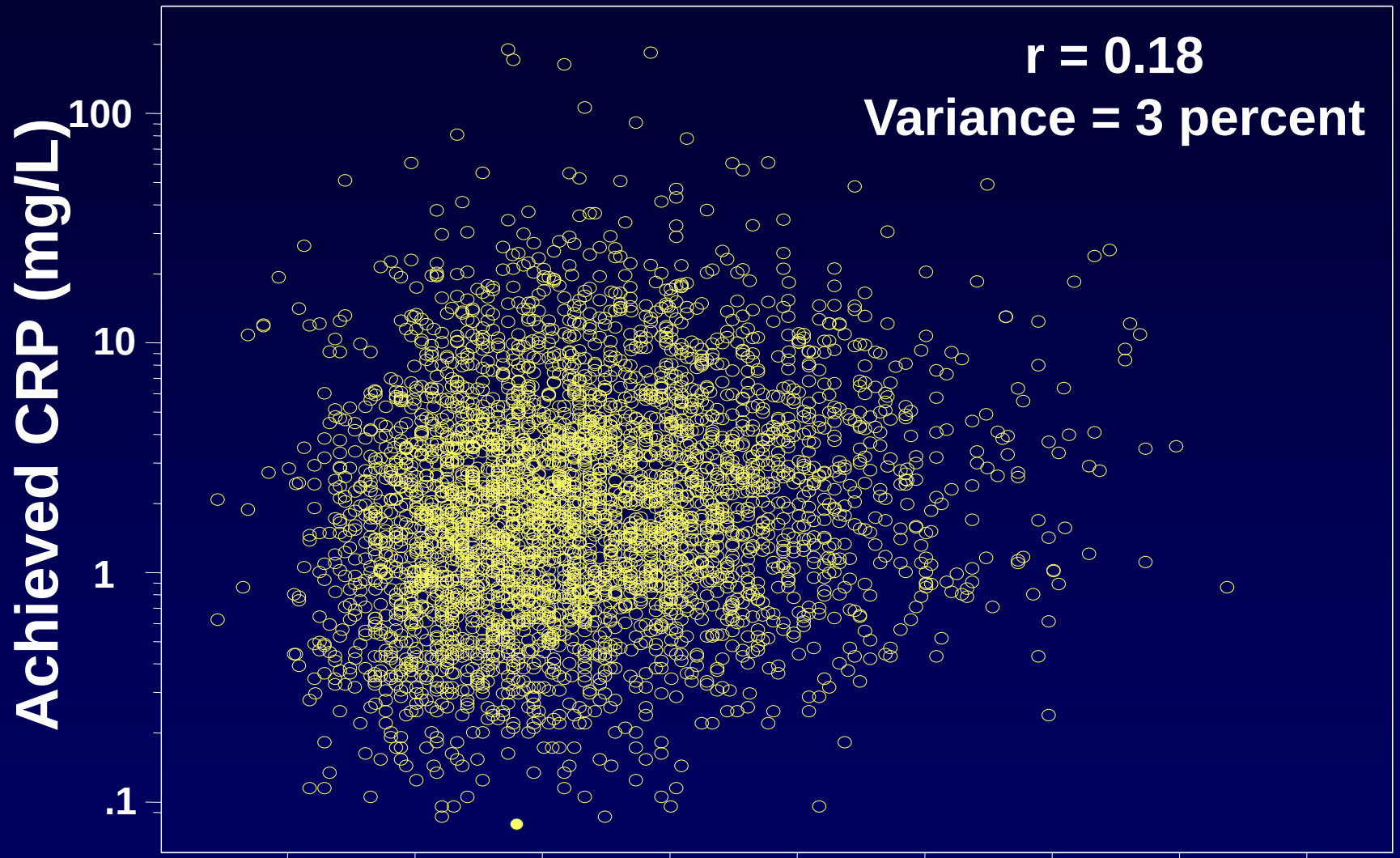
Ridker et al. NEJM 2005

Potential Pleiotropic Effects of Statins

- **Statins reduce C-reactive protein (CRP)- *but* the individual magnitude of CRP reduction does not correlate well with the drop in LDL-C levels**

Blake GJ et al. *Am J Cardiol* 2003;41:37S-42S.

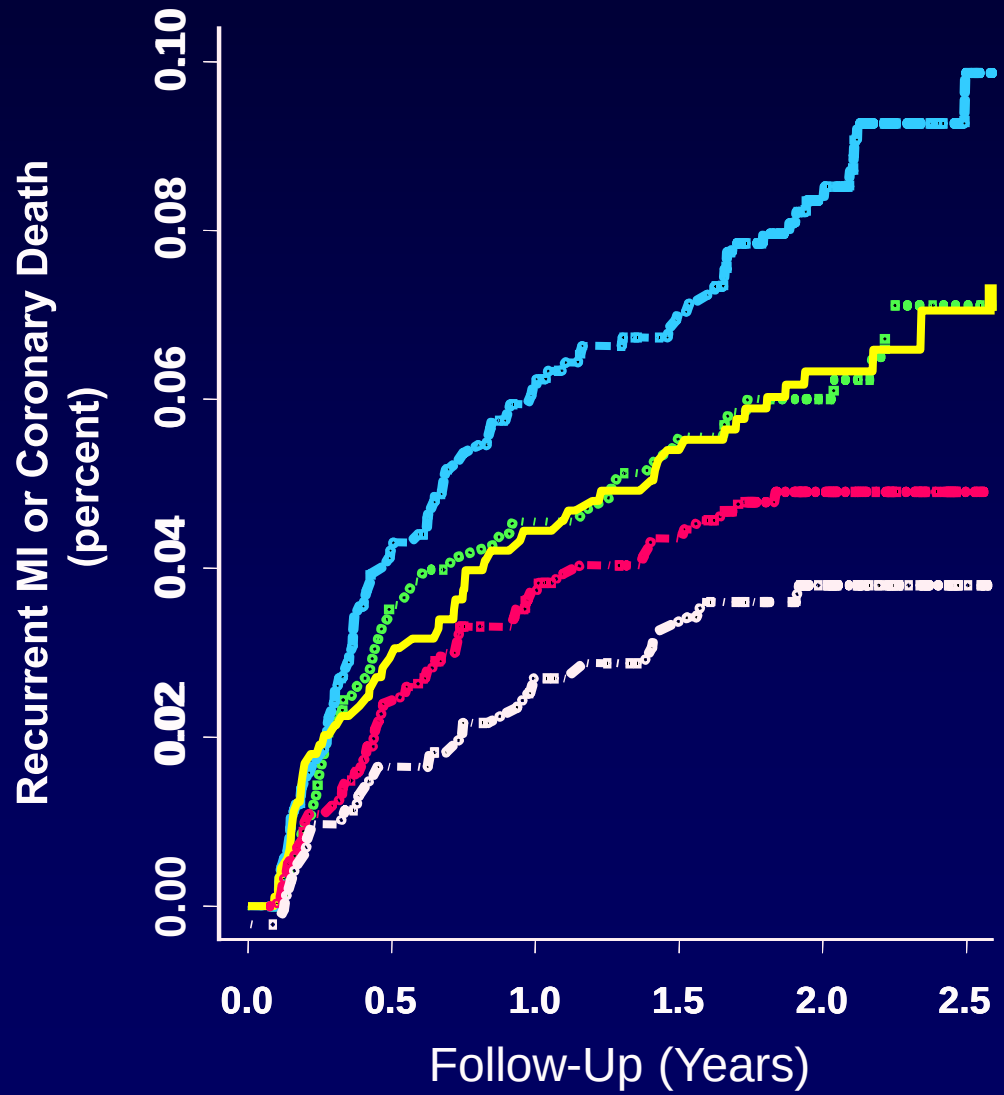
Minimal Relationship Between Achieved LDL and Achieved CRP After Initiation of Statin Therapy



Ridker *et al.*
NEJM 2005

PROVE IT – TIMI 22

Clinical Relevance of Achieved LDL and Achieved CRP After Treatment with Statin Therapy



LDL ≥ 70 mg/dL, CRP ≥ 2 mg/L

LDL ≥ 70 mg/dL, CRP < 2 mg/L

LDL < 70 mg/dL, CRP ≥ 2 mg/L

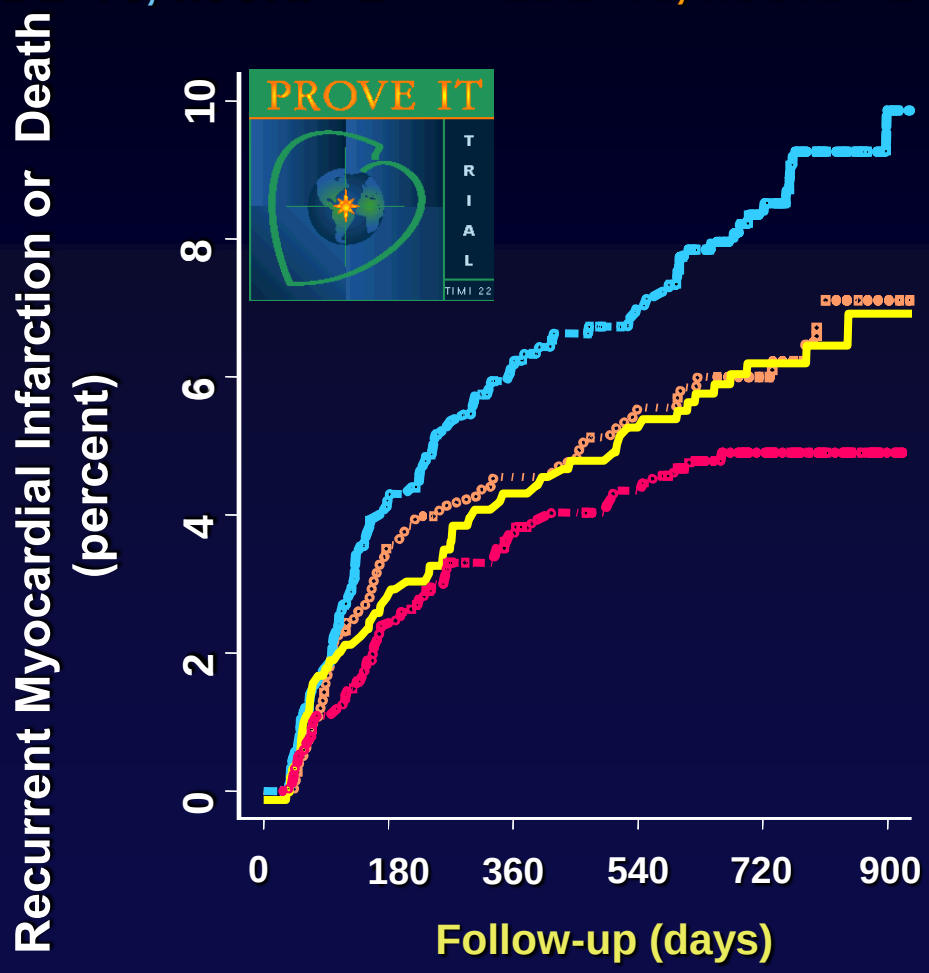
LDL < 70 mg/dL, CRP < 2 mg/L

LDL < 70 mg/dL, CRP < 1 mg/L

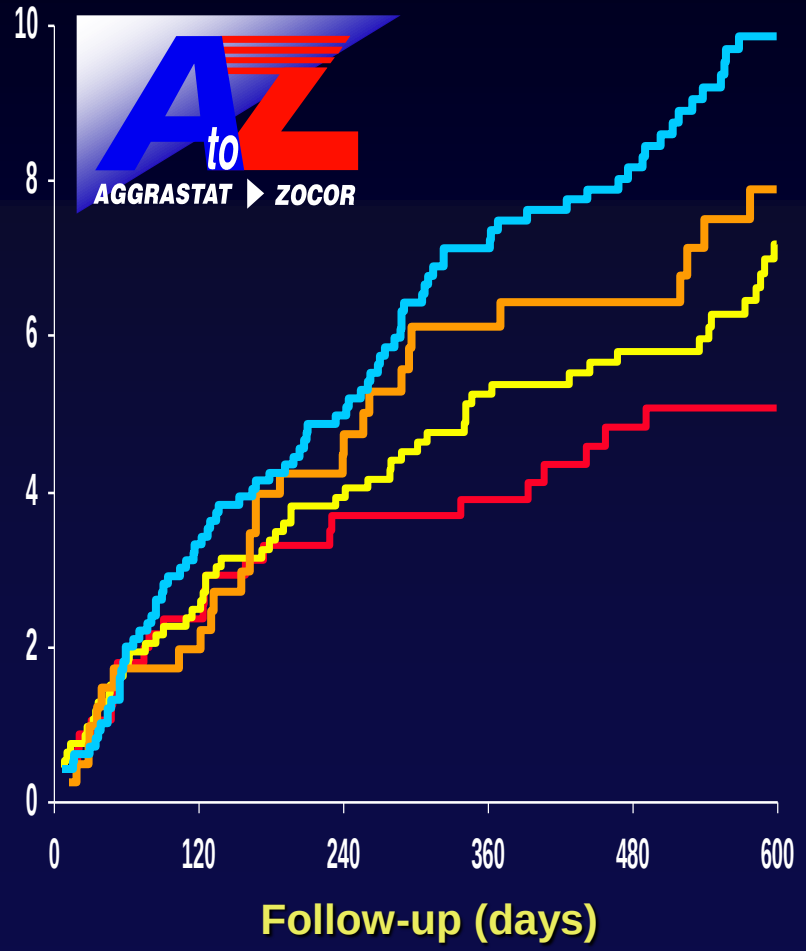
Ridker et al. NEJM 2005

Clinical Importance of Achieving LDL-C < 70 mg/dL and hsCRP < 2 mg/LFollowing Initiation of Statin Therapy

LDL>70, hsCRP>2 LDL<70, hsCRP>2 LDL>70, hsCRP<2 LDL<70, hsCRP<2



PROVE IT – TIMI 22
NEJM 2005;352:20-28.



A to Z
Circulation 2006;114:281-8

TIMI

JUPITER
Does clinical benefit associate with achieved LDLC, achieved hsCRP, or both?

Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial

Paul M Ridker, Eleanor Danielson, Francisco A H Fonseca, Jacques Genest, Antonio M Gotto Jr, John J P Kastelein, Wolfgang Koenig, Peter Libby, Alberto J Lorenzatti, Jean G MacFadyen, Børge G Nordestgaard, James Shepherd, James T Willerson, Robert J Glynn, on behalf of the JUPITER Trial Study Group

Summary

Background Statins lower high-sensitivity C-reactive protein (hsCRP) and cholesterol concentrations, and hypothesis generating analyses suggest that clinical outcomes improve in patients given statins who achieve hsCRP concentrations less than 2 mg/L in addition to LDL cholesterol less than 1·8 mmol/L (<70 mg/dL). However, the benefit of lowering both LDL cholesterol and hsCRP after the start of statin therapy is controversial. We prospectively tested this hypothesis.

www.thelancet.com Published online March 29, 2009

Published Online March 29, 2009 DOI:10.1016/S0140-6736(09)60447-5

See Online/Comment DOI:10.1016/S0140-6736(09)60448-7

JUPITER
LDL reduction, hsCRP reduction, or both?

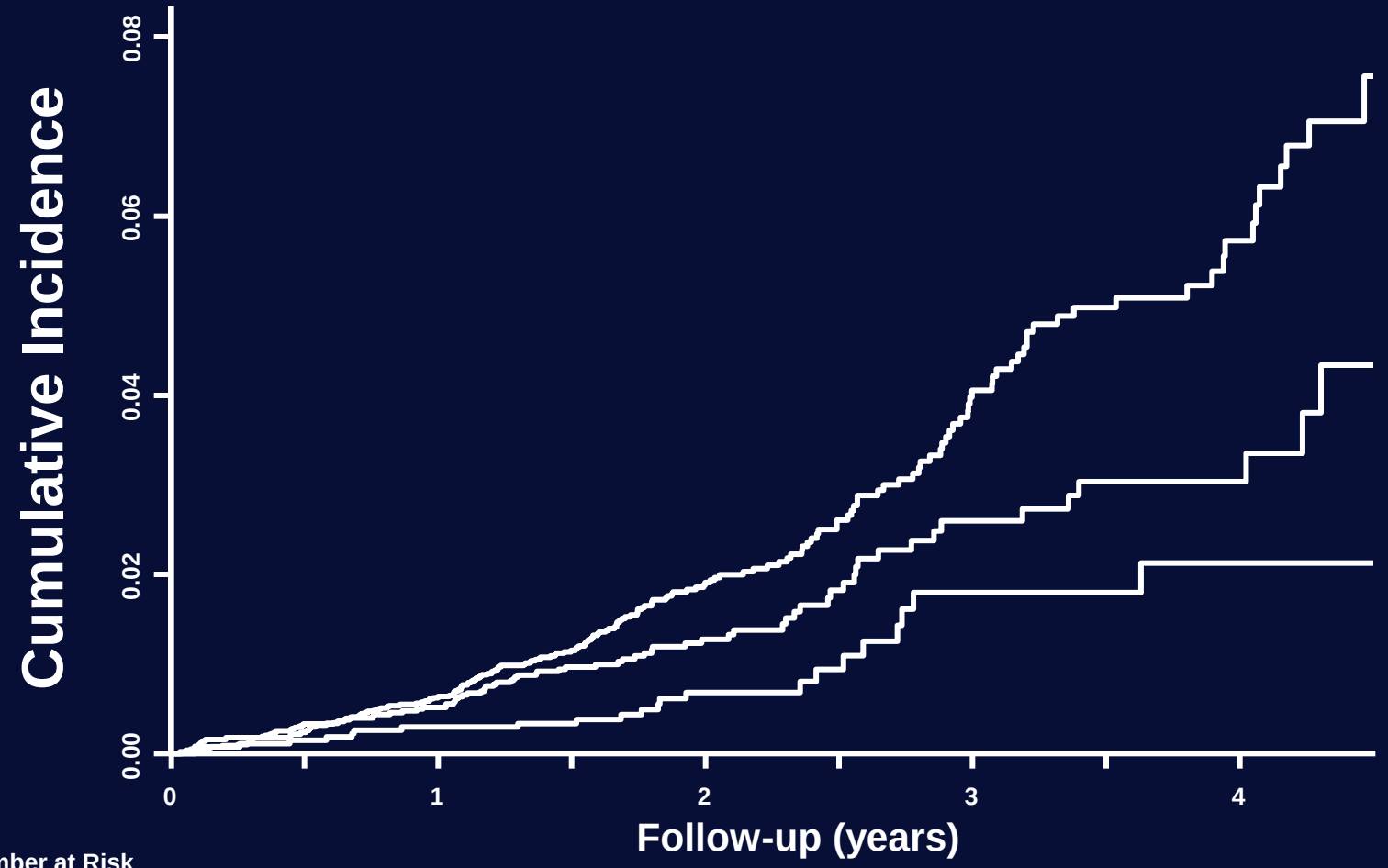
An *individual's* drop in LDL and drop in hsCRP on statin treatment vary *independently*

	r value
Achieved LDLC, Achieved hsCRP	0.10
Percent change in LDLC, Percent change in hsCRP	0.15

The variance in achieved LDLC explains less than 2 percent of the variance in achieved hsCRP

JUPITER

Dual Cutpoint Analysis: LDLC<70 mg/dL, hsCRP<2 mg/L



Placebo
HR 1.0 (referent)

LDL > 70 mg/dL
and / or
hsCRP > 2 mg/L
HR 0.64 (0.49-0.84)

LDL < 70 mg/dL
and
hsCRP < 2 mg/L
HR 0.35 (0.23-0.54)

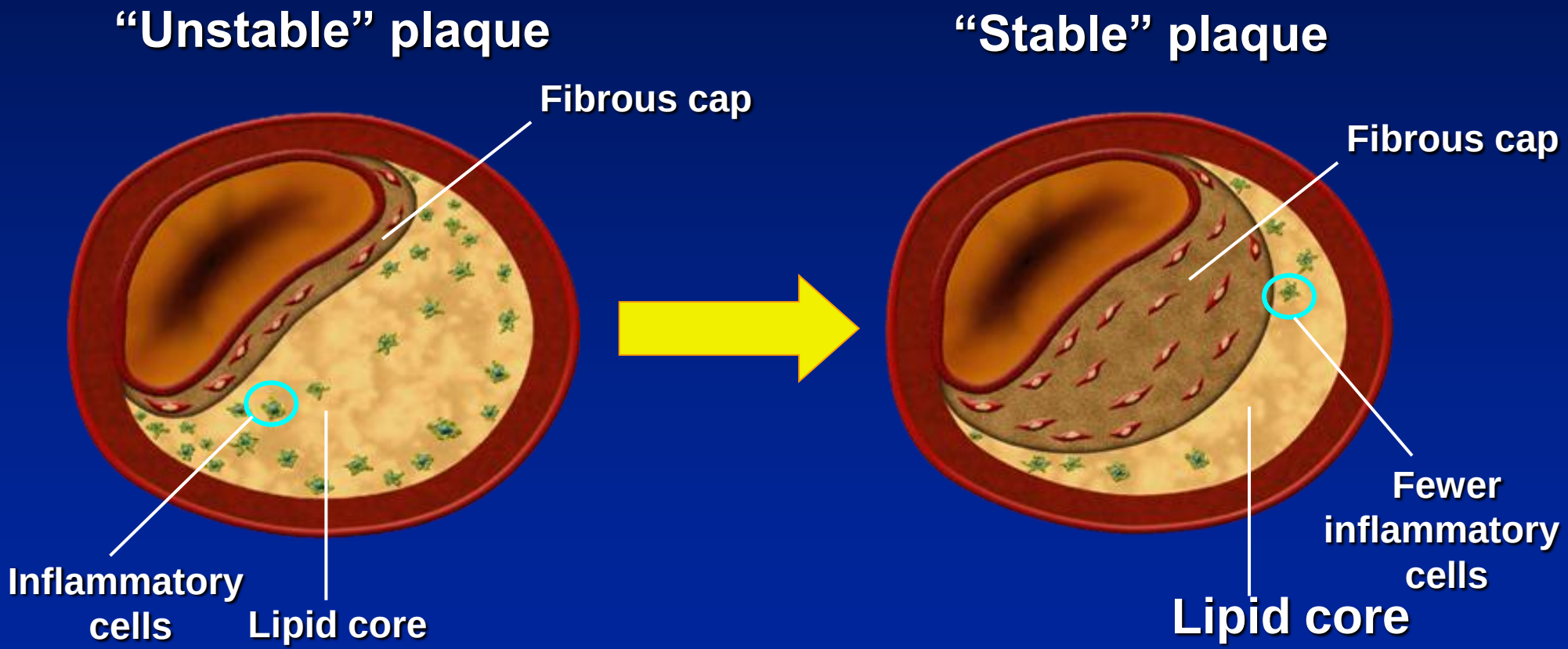
Number at Risk										
Rosuvastatin	7,716	7,699	7,678	6,040	3,608	1,812	1,254	913	508	145
Placebo	7,832	7,806	7,777	6,114	3,656	1,863	1,263	905	507	168

P < 0.0001

How might lipid lowering prevent cardiovascular events?

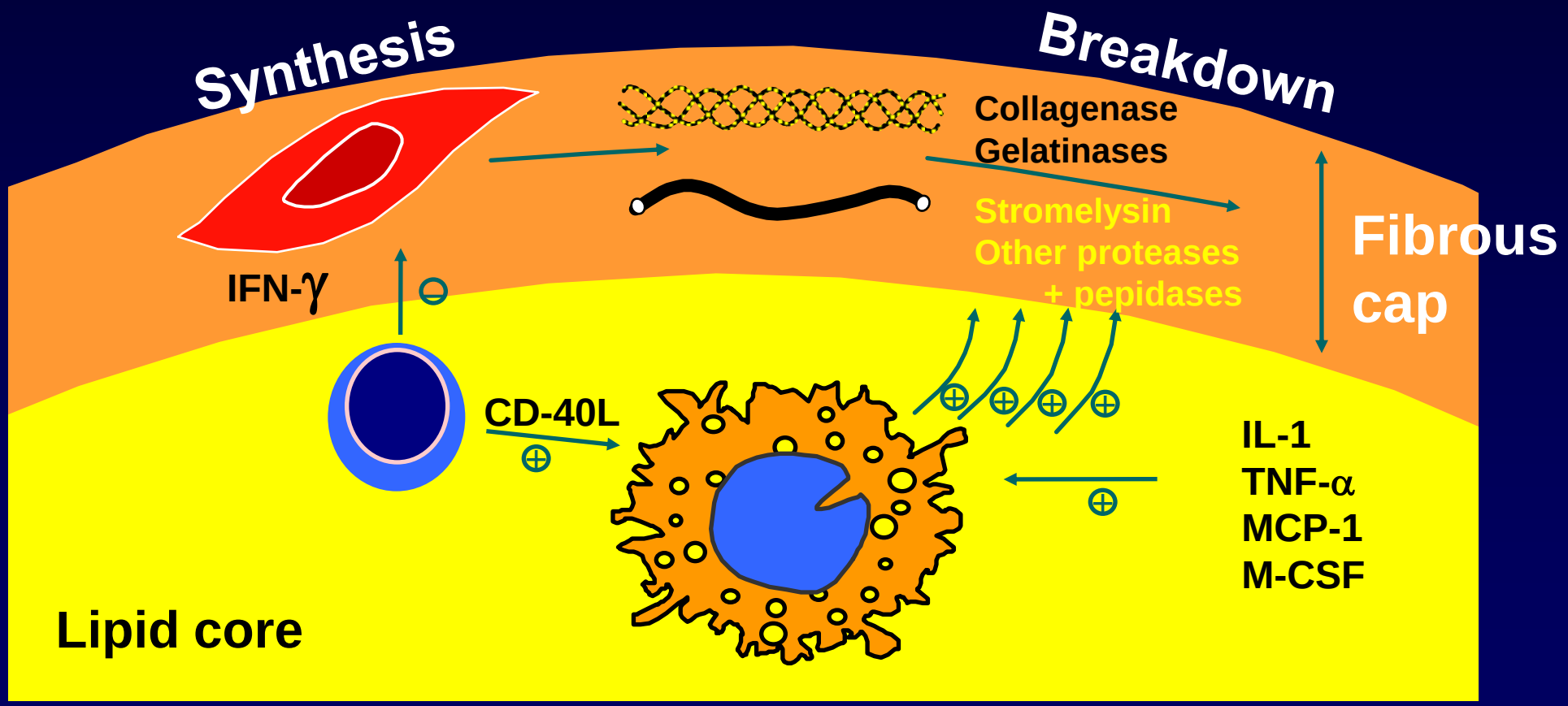
- Stabilizing the plaque's fibrous cap

Plaque "Stabilization": Plaques with a thick fibrous cap may have less tendency to rupture and cause thrombosis



After Libby P. *Circulation*. 1995;91:2844-2850.

Matrix metabolism and integrity of the plaque's fibrous cap

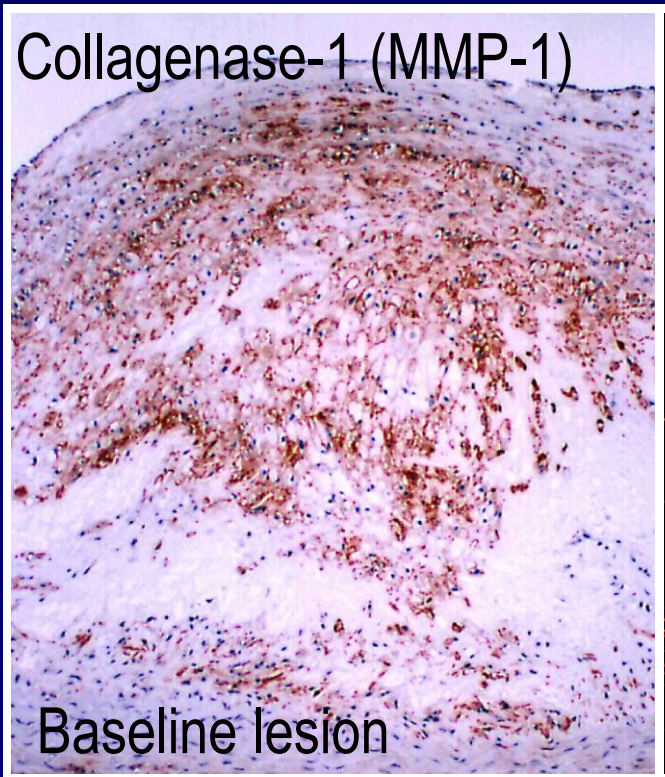


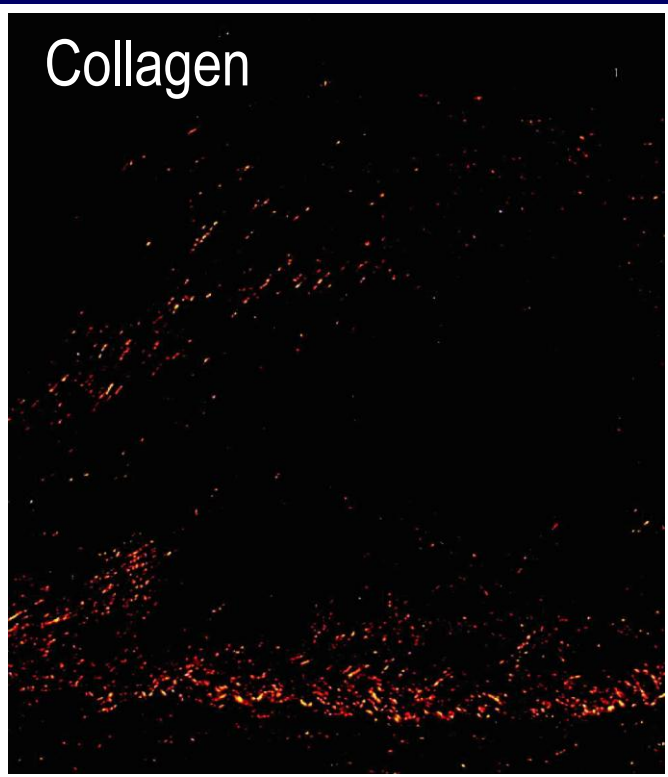
After Libby P. Circulation 1995

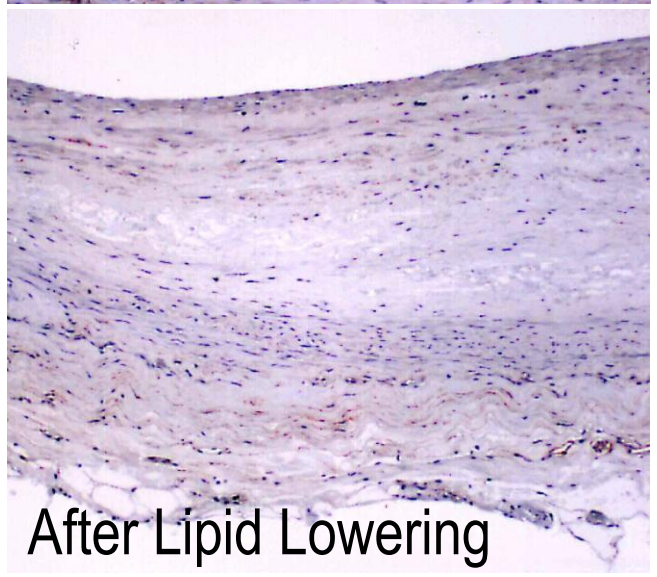
Lipid lowering reduces collagenase expression and increases collagen accumulation in rabbit atheroma

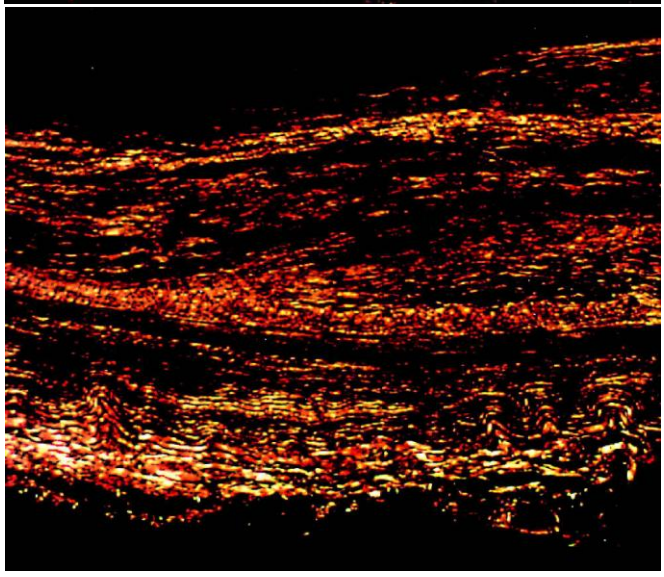
Masanori Aikawa,
Elena Rabkin,
Yoshikatsu Okada,
Sami J. Voglic,
Steven K. Clinton,
Constance E. Brinckerhoff,
Galina K. Sukhova,
Peter Libby

Circulation 1998;97:2433







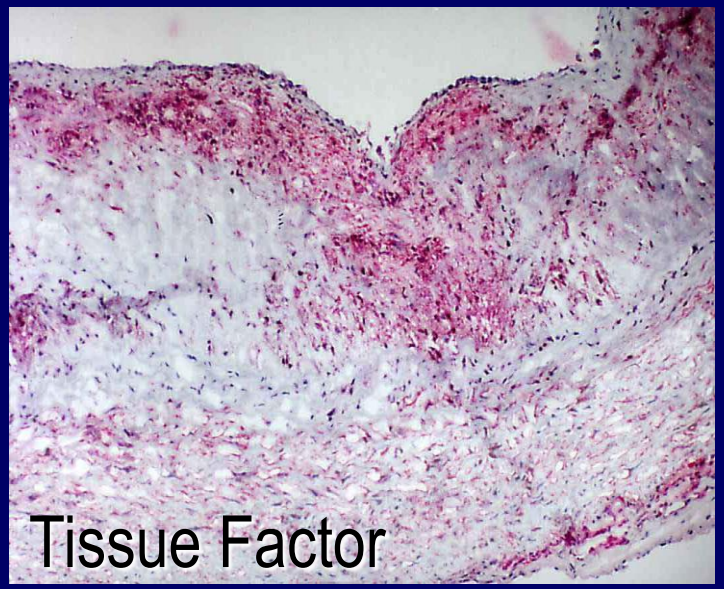


Lipid Lowering Reduces Plaque Tissue Factor Expression

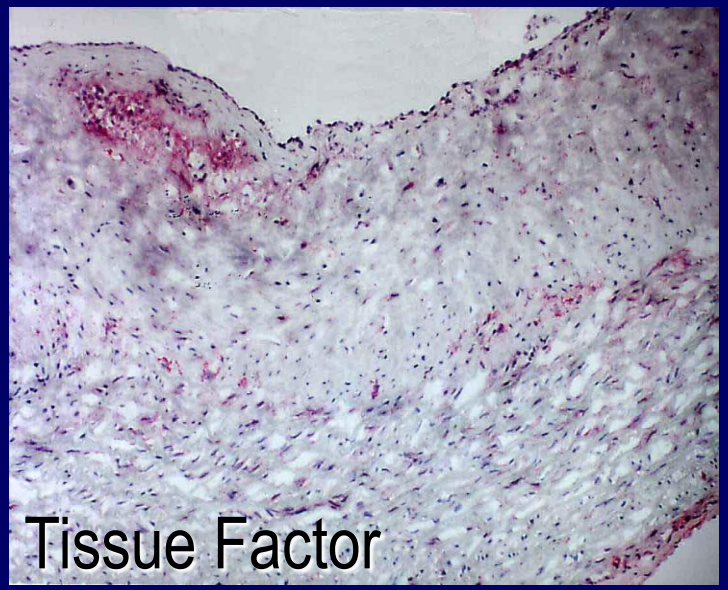
Lipid lowering by diet Aikawa M, Voglic SJ, Sugiyama S, Rabkin E, Taubman MB, *Fallon JT, Libby P. Circulation 1999*

Lipid lowering by statin *Aikawa M, Rabkin E, Sugiyama S, Voglic SJ, Fukumoto Y, Furukawa Y, Shiomi M, Schoen FJ, Libby P. Circulation 2001*

Control group



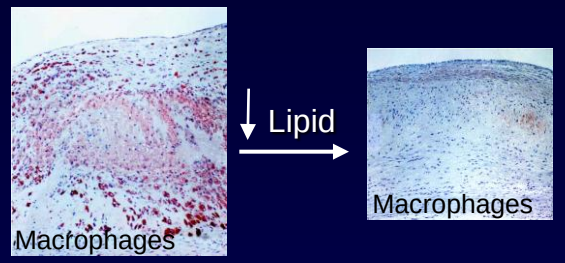
Lipid-lowered group



Plaque "stabilization" by lipid lowering: *an anti-inflammatory therapy*

Cholesterol ↓ by diet →

- Macrophage accumulation ↓
- MMP-1, -2, -3, -9 expression ↓
- Collagen accumulation ↑
- Tissue factor expression/activity ↓
- CD40L / CD40 expression ↓
- PDGF-B expression ↓
- SMC maturation/differentiation ↑
- LDL accumulation ↓
- oxLDL/oxPL accumulation ↓
- Anti-oxLDL autoantibody ↓
- ROS production ↓
- VCAM-1 expression ↓
- MCP-1 expression ↓
- eNOS expression ↑
- Microvessels ↓

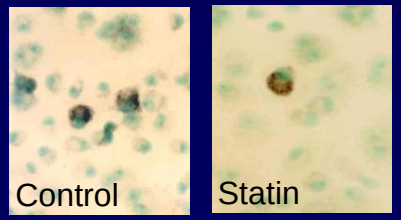


Aikawa et al. Circulation '98
Aikawa et al. Circ Res '98
Aikawa et al. Circulation '99
Aikawa et al. Circulation '02
Aikawa et al. CV Pathol '04
Tsimikas et al. ATVB '06

Cholesterol ↓ by statins →

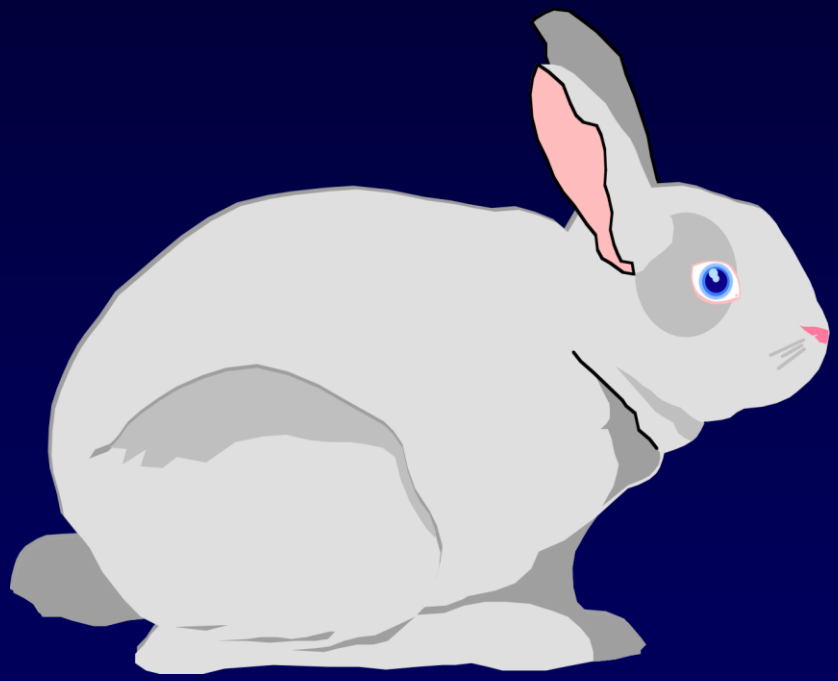
- Macrophage accumulation/growth ↓
- MMP-1, -3, -9 expression ↓
- Collagen accumulation ↑
- Tissue factor expression ↓
- CD40L / CD40 expression ↓
- PAI-I expression ↓
- oxLDL accumulation ↓

↓ Macrophage growth



Aikawa et al. Circulation '01
Fukumoto et al. Circulation '01

How can we translate inflammation biology to the clinic?



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Clinical Evidence for Statin Treatment Increasing Fibrous vs. Lipid Character of Atherosclerotic Plaques

Journal of the American College of Cardiology
Vol. 46, No. 11, 2005

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doi:10.1016/j.jacc.2005.04.070

Atherosclerosis Evaluation by Ultrasound

Stabilization of Carotid Atheroma Assessed by Quantitative Ultrasound Analysis in Nonhypercholesterolemic Patients With Coronary Artery Disease

Keisuke Watanabe, MD,* Seigo Sugiyama, MD, PHD,* Kiyotaka Kugiyama, MD, PHD,‡ Osamu Honda, MD,* Hironobu Fukushima, MD,* Hidenobu Koga, MD,* Yoko Horibata, MD,* Toshinori Hirai, MD, PHD,† Tomohiro Sakamoto, MD, PHD,* Michihiro Yoshimura, MD, PHD,* Yasuyuki Yamashita, MD, PHD,† Hisao Ogawa, MD, PHD*

Kumamoto and Yamanashi, Japan

Stabilization of carotid atheroma assessed by quantitative ultrasound analysis in nonhypercholesterolemic patients with coronary artery disease.

Watanabe et al. JACC 2005;46:2022-30

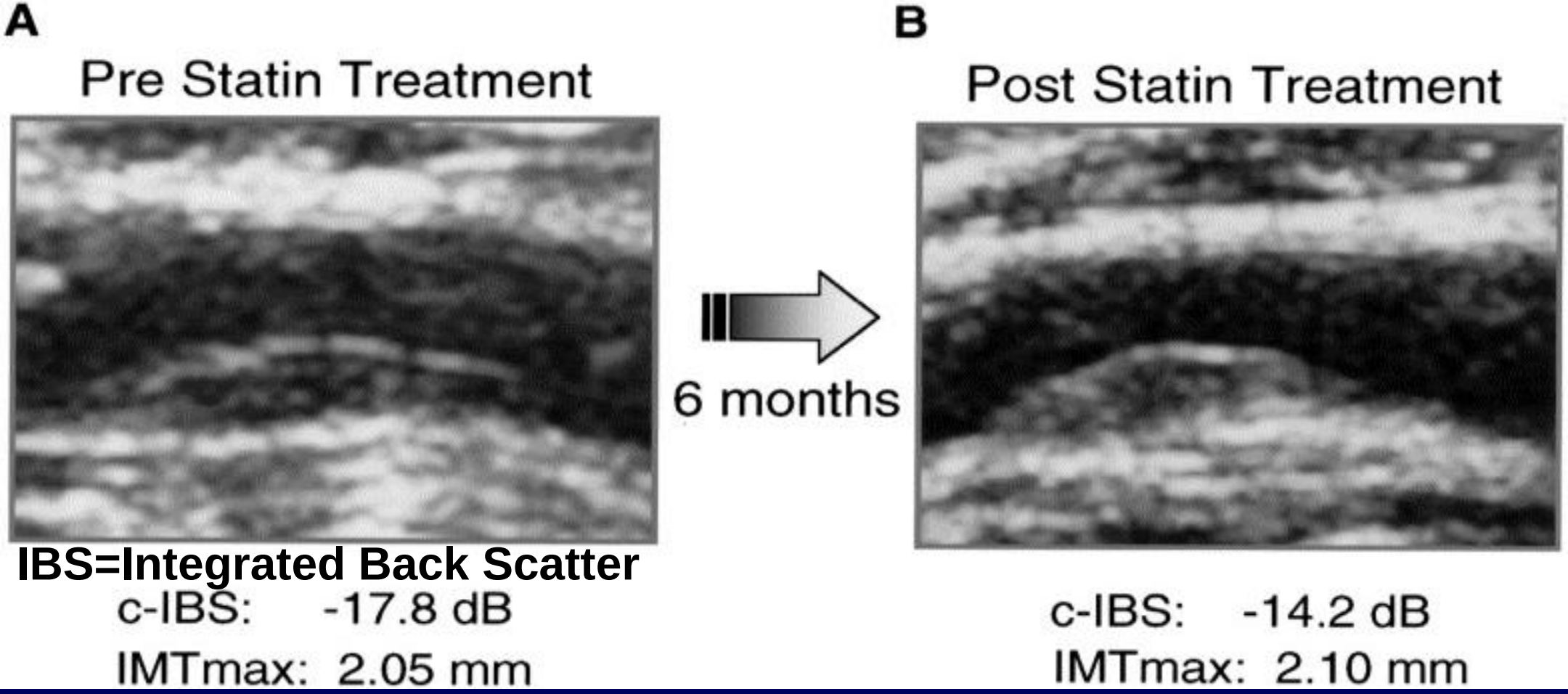
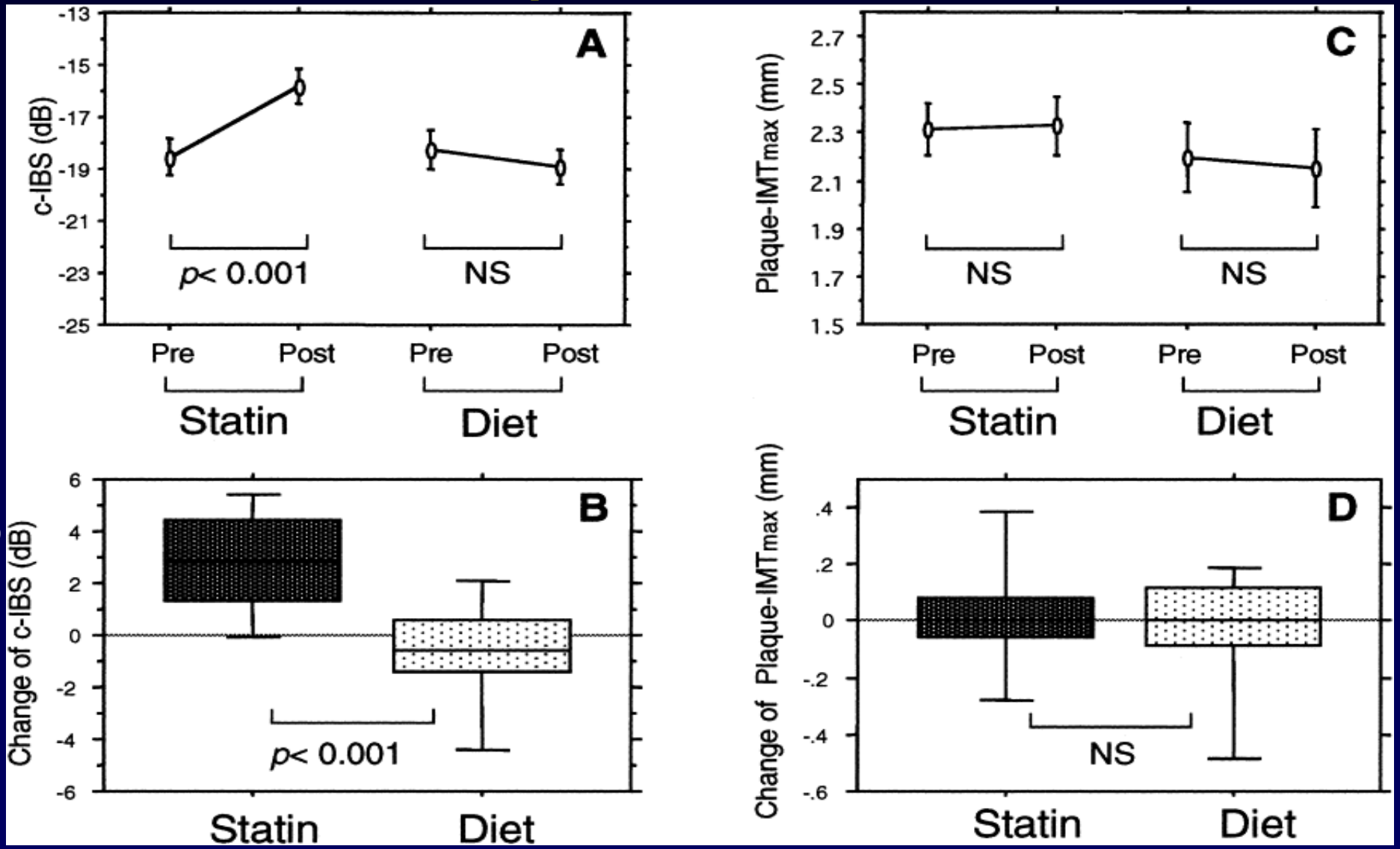


Figure 4. Representative IBS images of carotid atheroma from baseline to follow-up. (A) Carotid atheroma at pretreatment. Values of cIBS and plaque-IMT_{max} of this plaque are −17.8 dB and 2.05 mm, respectively. (B) The same carotid atheroma post-pravastatin therapy (6 months). Values of cIBS and plaque-IMT_{max} of this plaque are −14.2 dB and 2.10 mm, respectively.

Statin Treatment Increases Fibrous Character of Atherosclerotic Plaques but not Intima-Media Thickness

IBS = Integrated Back Scatter



IMT = Intima-Media Thickness

Watanabe K, Sugiyama S, Kugiyama K, et al. Stabilization of carotid atheroma assessed by quantitative ultrasound analysis in nonhypercholesterolemic patients with coronary artery disease. J Am Coll Cardiol 2005;46:2022-30.

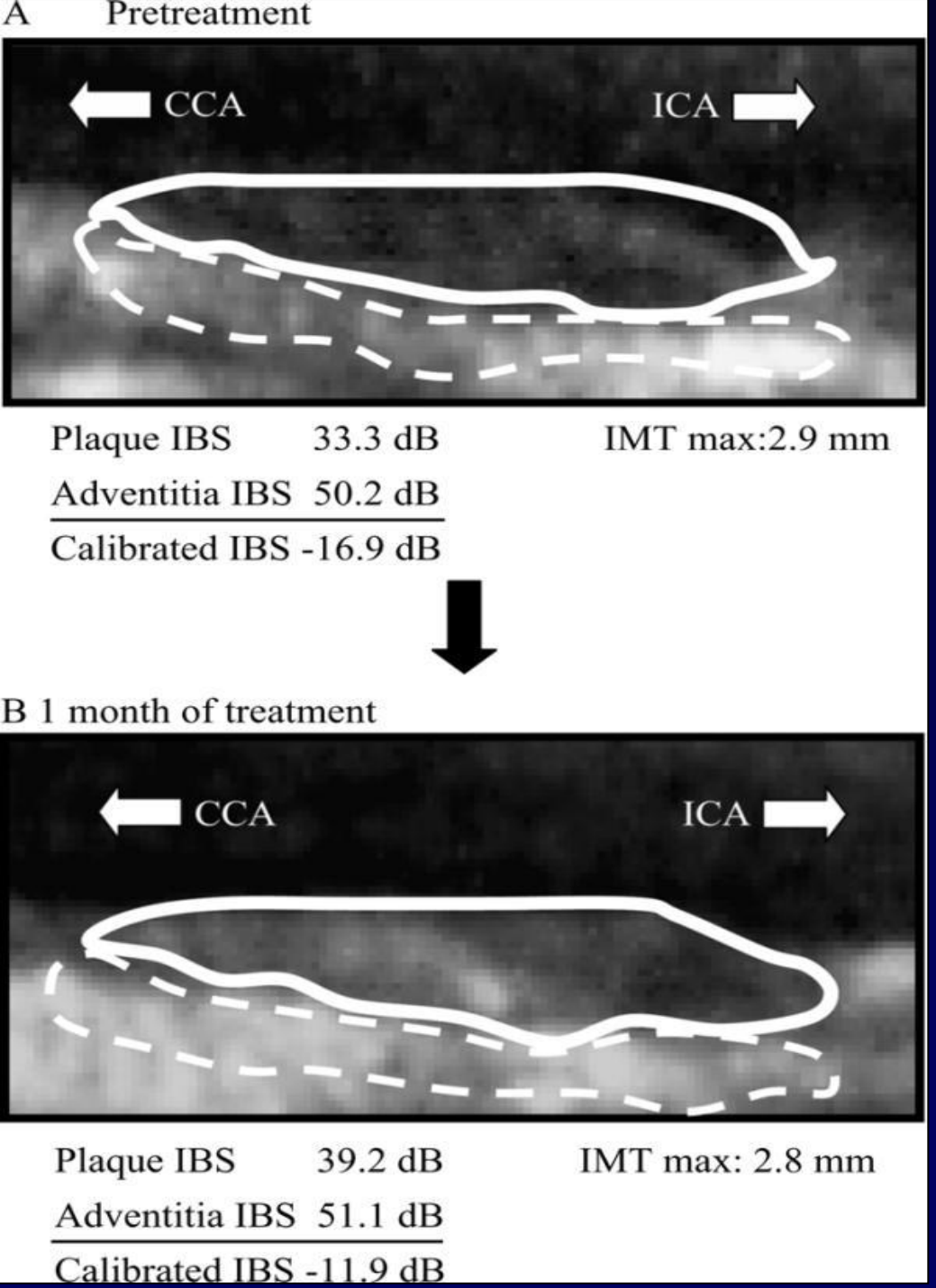
Rapid Stabilization of Vulnerable Carotid Plaque Within 1 Month of Pitavastatin Treatment in Patients With Acute Coronary Syndrome

Takamitsu Nakamura, MD, Jun-ei Obata, MD, PhD, Yoshinobu Kitta, MD, PhD, Hajime Takano, MD, PhD, Tsuyoshi Kobayashi, MD, Daisuke Fujioka, MD, PhD, Yukio Saito, MD, Yasushi Kodama, MD, Kenichi Kawabata, MD, PhD, Akira Mende, MD, Toshiaki Yano, MD, Mitsumasa Hirano, MD, Keita Sano, MD, Kazuto Nakamura, MD, PhD, and Kiyotaka Kugiyama, MD, PhD

Abstract: We determined time course of stabilization of echolucent carotid plaques by statin therapy in patients with acute coronary syndrome (ACS). Treatment with 4 mg/d pitavastatin (n = 33) or placebo (n = 32) was initiated within 3 days after onset of ACS in 65 patients with echolucent carotid plaque. Vulnerable carotid plaques were assessed by measuring plaque echolucency using carotid ultra- sound with integrated backscatter (IBS) analysis before and 1 month after treatment in all patients. The calibrated IBS value (intima-media IBS value minus adventia IBS) of vulnerable carotid plaques favorably changed at 1 month after treatment in both groups, but the echo- lucency at 1 month improved more in the pitavastatin than in the placebo group (pitavastatin group: –18.7 6 3.3 dB at pretreatment versus –12.7 6 2.3 dB at 1 month *P , 0.001; placebo: –19.0 6 3.5 dB versus –16.9 6 3.2 dB, P , 0.05, *P , 0.01 versus the value at 1 month in placebo group). Levels of CRP, VEGF, and TNFa at 1 month were significantly lower in pitavastatin than placebo group. In conclusion, pitavastatin improved carotid plaque echolucency within 1 month of therapy in patients with ACS, in association with decrease in the inflammatory biomarkers related to vulnerable plaques.

(J Cardiovasc Pharmacol 2008;51:365–371)

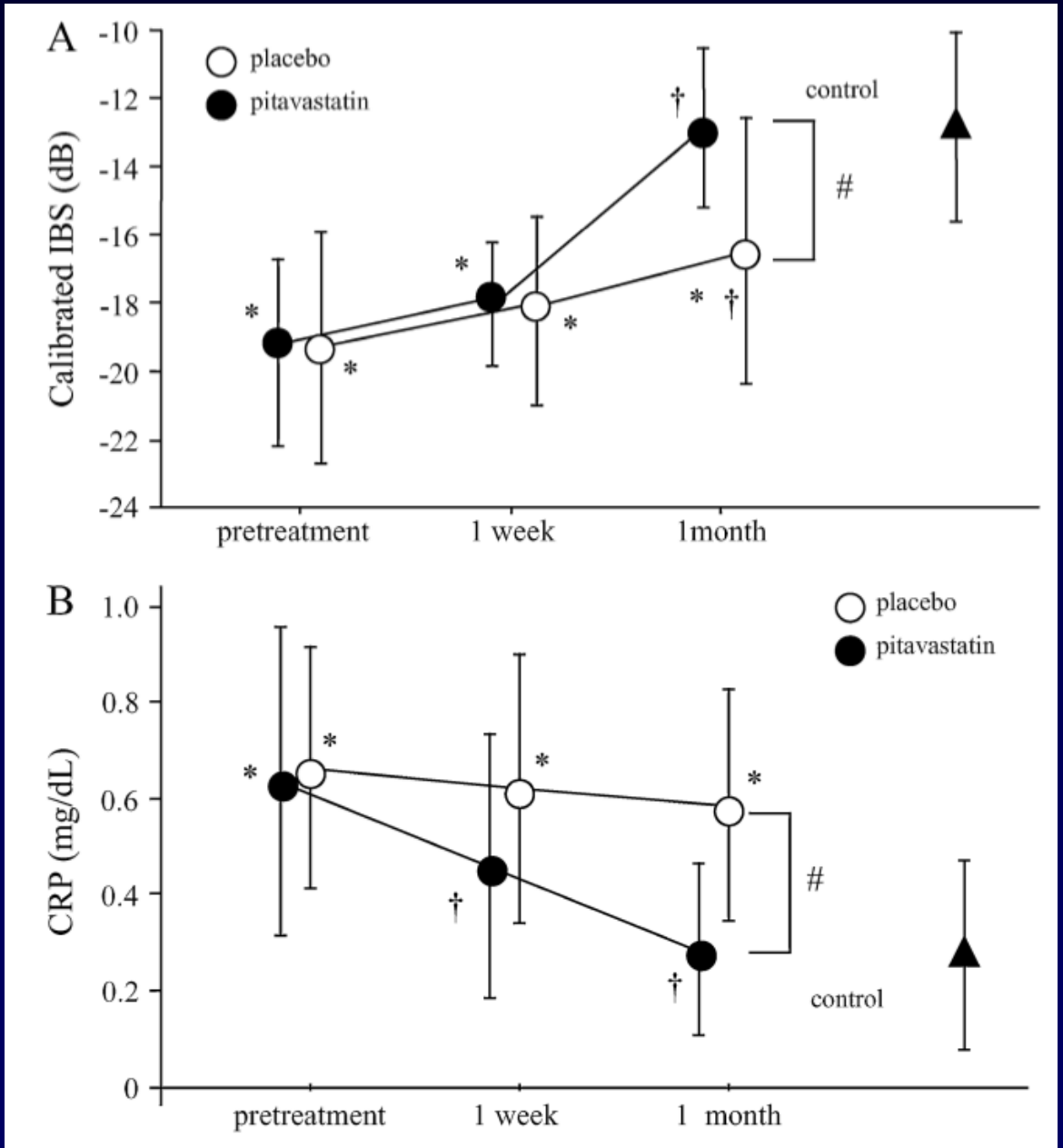
Rapid Stabilization of Vulnerable Carotid Plaque Within 1 Month of Pitavastatin Treatment in Patients With Acute Coronary Syndrome



Representative IBS images of carotid atheroma from pretreatment to 1-month treatment with pitavastatin. A, Carotid atheroma at pretreatment. B. The same carotid atheroma after 1-month treatment with pitavastatin. The white line indicates the region of interest (ROI) in the plaque (intima-media complex), and the white dotted line indicates the ROI in the adventitia using the manual outline definition mode. CCA, common carotid artery; IBS, integrated backscatter; ICA, internal carotid artery; IMT, intima-media thickness.

Nakamura *et al.* Journal of Cardiovascular Pharmacology. 51:365-371; 2008.

Rapid Stabilization of Vulnerable Carotid Plaque Within 1 Month of Pitavastatin Treatment in Patients With ACS

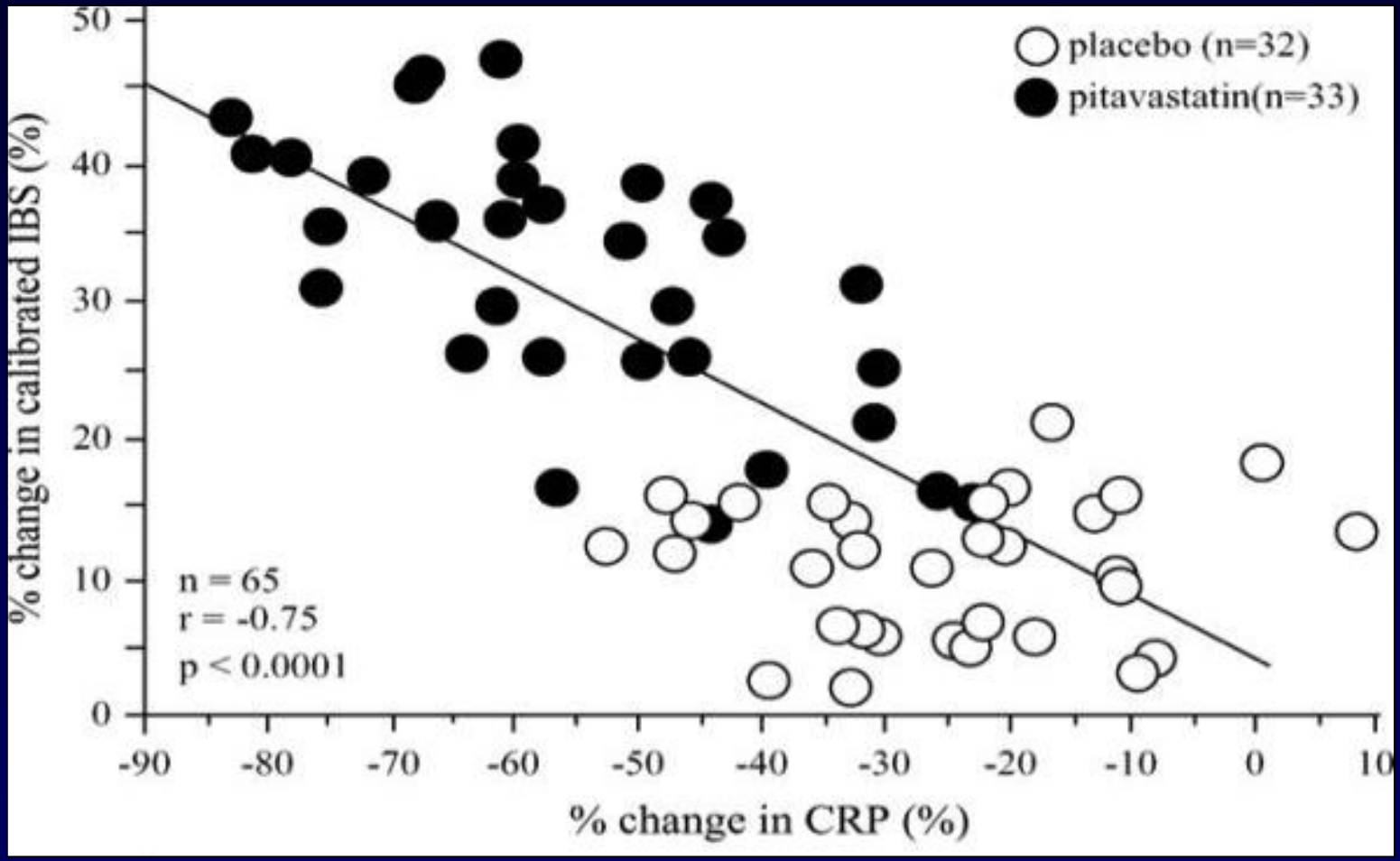


Comparison between pitavastatin (n = 33) and placebo (n = 32) treatment on calibrated integrated backscatter (IBS) levels A, and CRP levels B. Mean +/- SD.

*P < 0.01 between pitavastatin and placebo groups using 2-way ANOVA.

Nakamura, et al. Journal of Cardiovascular Pharmacology. 51:365-371; 2008.

Rapid Stabilization of Vulnerable Carotid Plaque Within 1 Month of Pitavastatin Treatment in Patients With ACS



Relationship of the percent change in calibrated IBS values with the percent change in CRP levels from baseline to 1 month of follow-up.

Nakamura, et al. Journal of Cardiovascular Pharmacology. 51:365-371; 2008.

Possible Non-LDL Lowering Effects of Statins Relevant to Atherosclerosis

- Reducing thrombogenicity
- Opposing vasospasm
- Decreasing inflammation
- Stabilizing fibrous cap

What is the molecular basis of statins' LDL-independent effects?

A Molecular Mediator of Statins' "Pleiotropic" Effects: the Transcriptional Regulator Kruppel-like Factor-2 (KLF-2)

Krupple-like factor 2 (KLF-2) Antagonizes Cytokine-Induced Endothelial Activation and Promotes Vasculoprotective Gene Expression

Cytokine → E-selectin, VCAM-1, ICAM-1, tissue factor, PAI-1 → pro-adhesive, pro-coagulant, anti-fibrinolytic

KLF2 Inhibits

Laminar Flow → eNOS, thrombomodulin, PGI_2, tPA, Superoxide dismutase → anti-adhesive, anti-coagulant, anti-oxidant

KLF2 Stimulates

Statins Exert Endothelial Atheroprotective Effects via the KLF2 Transcription Factor*

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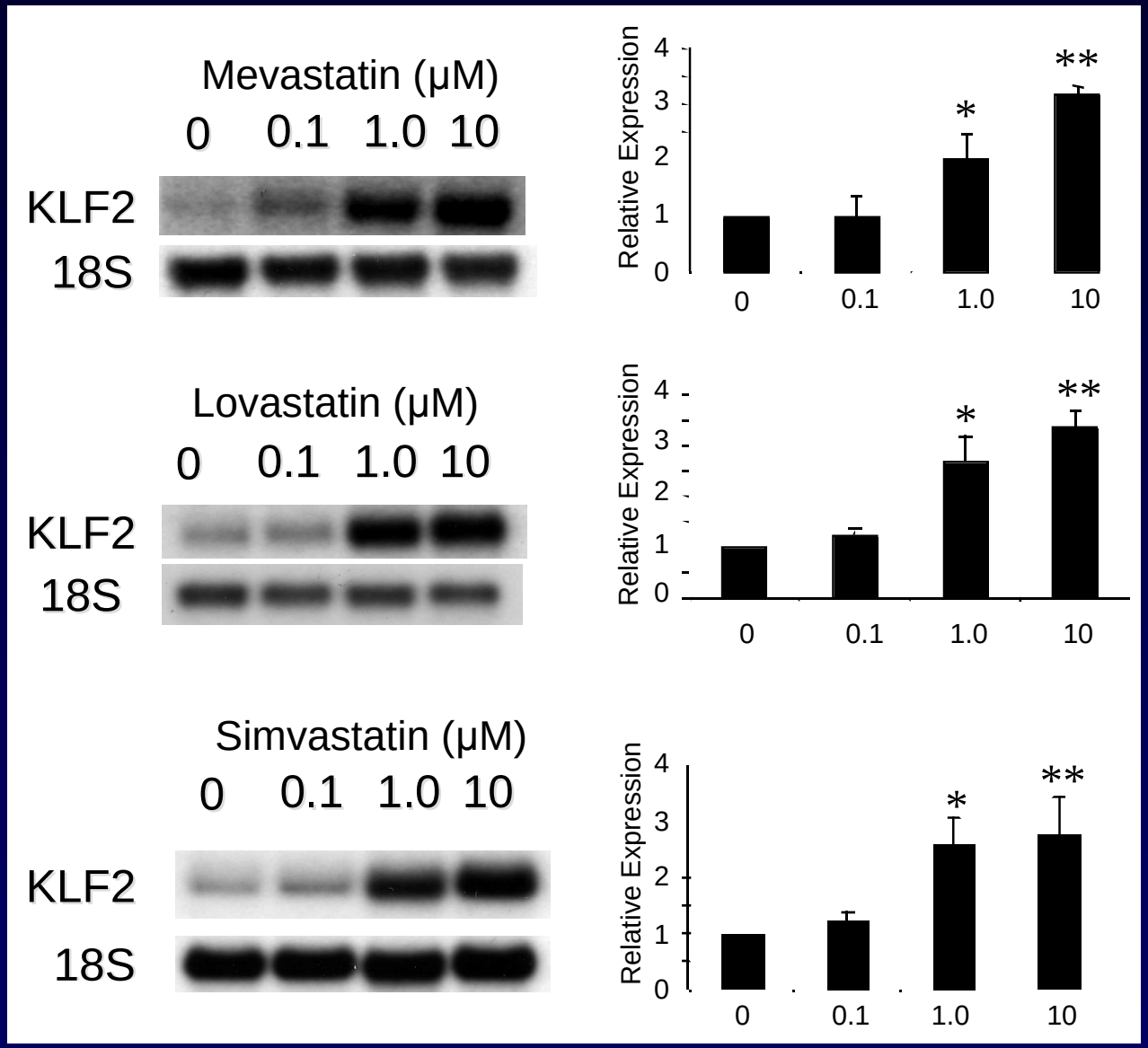
J. Biol.Chem. 280:26714-19 (May, 2005)

Statins raise KLF2 levels



(SenBanerjee, Circulation, 2005)

(Slide courtesy of M. Jain)

Do statins affect adaptive as well as innate immunity?

Statins as a newly recognized type of immunomodulator

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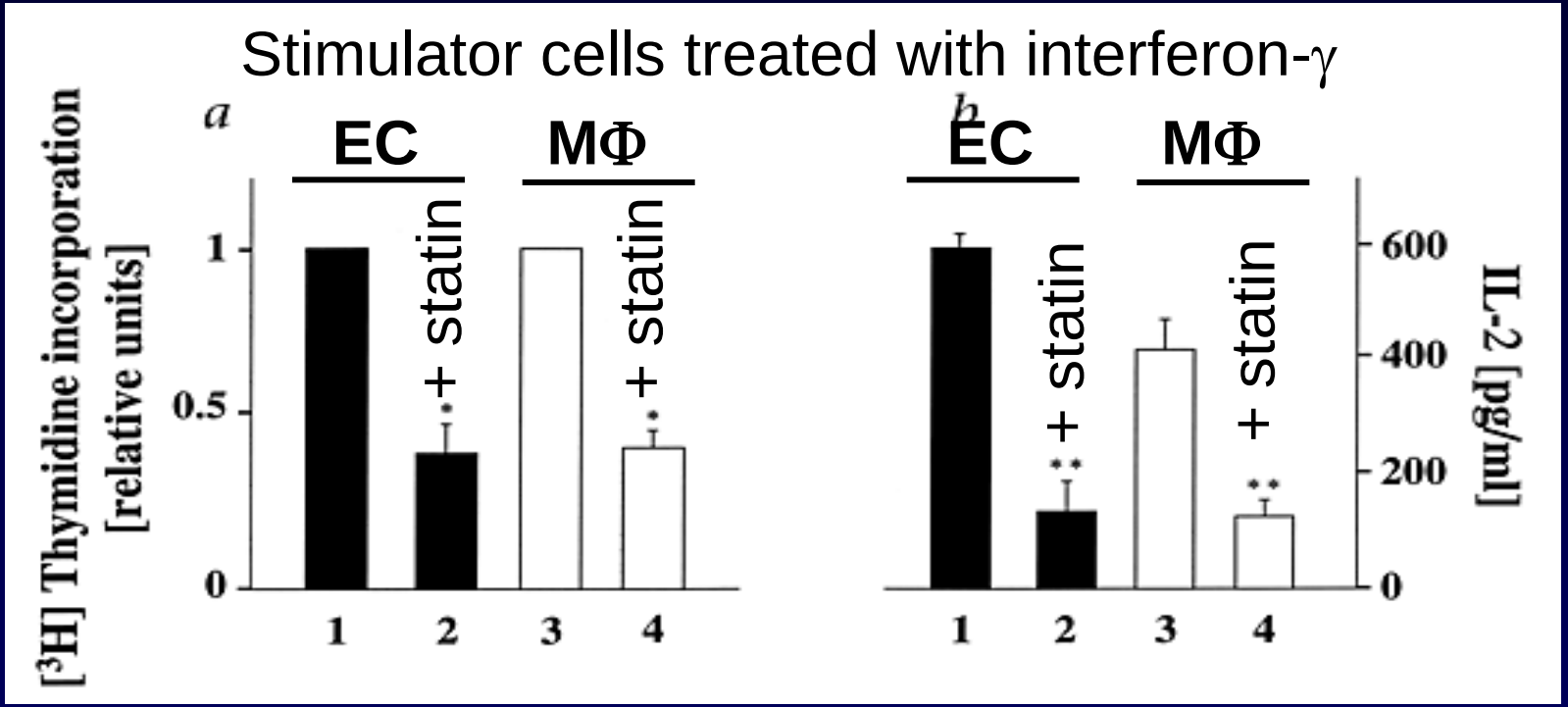
Inhibition of MHC-II antigens by statins reduces T-lymphocyte proliferation and interleukin-2 production



a, [3H]Thymidine incorporation measured in allogeneic T lymphocytes exposed (five days) to human ECs or Mφ pretreated for 48 h with IFN-γ (500 U/ml) alone, or IFN-γ (500 U/ml) with Atorvastatin (10 μM). Similar results were obtained in independent experiments with ECs or Mφ from three different donors. *$P < 0.02$ compared to IFN-γ treated cells. ***b***, IL-2 release measured by ELISA in supernatants of allogeneic T lymphocytes exposed (48 h) to human ECs (□) or Mφ (□) pre-treated during 48 h with IFN-γ (500 U/ml) alone, or IFN-γ (500 U/ml) with Atorvastatin (10 μM). Similar results were obtained in independent experi- ments with ECs or Mφ from four different donors. **$P < 0.01$ compared to IFN-γ treated cells.

Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med 2000; 6 (12): 1399-1402.

Direct Anti-Inflammatory Mechanisms Contribute to Attenuation of Experimental Allograft Arteriosclerosis by Statins

Koichi Shimizu, MD, PhD; Masanori Aikawa, MD, PhD; Kiyoshi Takayama, PhD;
Peter Libby, MD; Richard N. Mitchell, MD, PhD

Background—Despite the development of effective immunosuppressive therapy, transplant graft arterial disease (GAD) remains the major limitation to long-term graft survival. The interplay between host inflammatory cells and donor vascular wall cells results in an intimal hyperplastic lesion, which leads to ischemia and graft failure. HMG-CoA reductase inhibitors (statins) reduce GAD in human cardiac allografts, although it is unclear whether this is secondary to cholesterol lowering or other mechanisms. This study tested the hypothesis that statins can suppress GAD by cholesterol-independent pathways.

Methods and Results—We performed heterotopic murine cardiac transplants in total allogeneic or major histocompatibility complex class II–mismatched combinations. Transplanted animals received either control chow, chow containing 25 ppm cerivastatin (low dose), or chow containing 125 ppm cerivastatin (high dose). Mean plasma cerivastatin concentrations were 0.0 (control), 10.1 (low dose), and 21.9 (high dose) nmol/L, respectively. Plasma cholesterol levels were the same in all groups. GAD scores decreased in low-dose ($P<0.05$) and high-dose ($P<0.0001$) cerivastatin groups compared with controls, with concomitant reduction in graft-infiltrating cells and significantly decreased intragraft RANTES and monocyte chemotactic protein-1 mRNA expression. Cerivastatin, as well as other statins, also reduced RANTES and monocyte chemotactic protein-1 production in mouse endothelial cells stimulated with interferon-γ and tumor necrosis factor-α in vitro.

Conclusions—Clinically achievable levels of an HMG-CoA reductase inhibitor attenuate GAD in murine heart transplants, diminish host inflammatory cell recruitment, and do not alter cholesterol levels. These results indicate that statins can affect arterial biology and inflammation independently of their effects on cholesterol metabolism. (***Circulation*. 2003; 108:2113-2120.**)

Statin-induced Kruppel-like factor 2 expression in human and mouse T cells reduces inflammatory and pathogenic responses

De-xiu Bu,[1] Margarite Tarrio,[1] Nir Grabie,[1] Yuzhi Zhang,[1] Hiroyuki Yamazaki,[2] George Stavrakis,[1] Elena Maganto-Garcia,[1] Zachary Pepper-Cunningham,[1] Petr Jarolim,[1] Masanori Aikawa,[2] Guillermo García-Cardeña,[1] and Andrew H. Lichtman[1]

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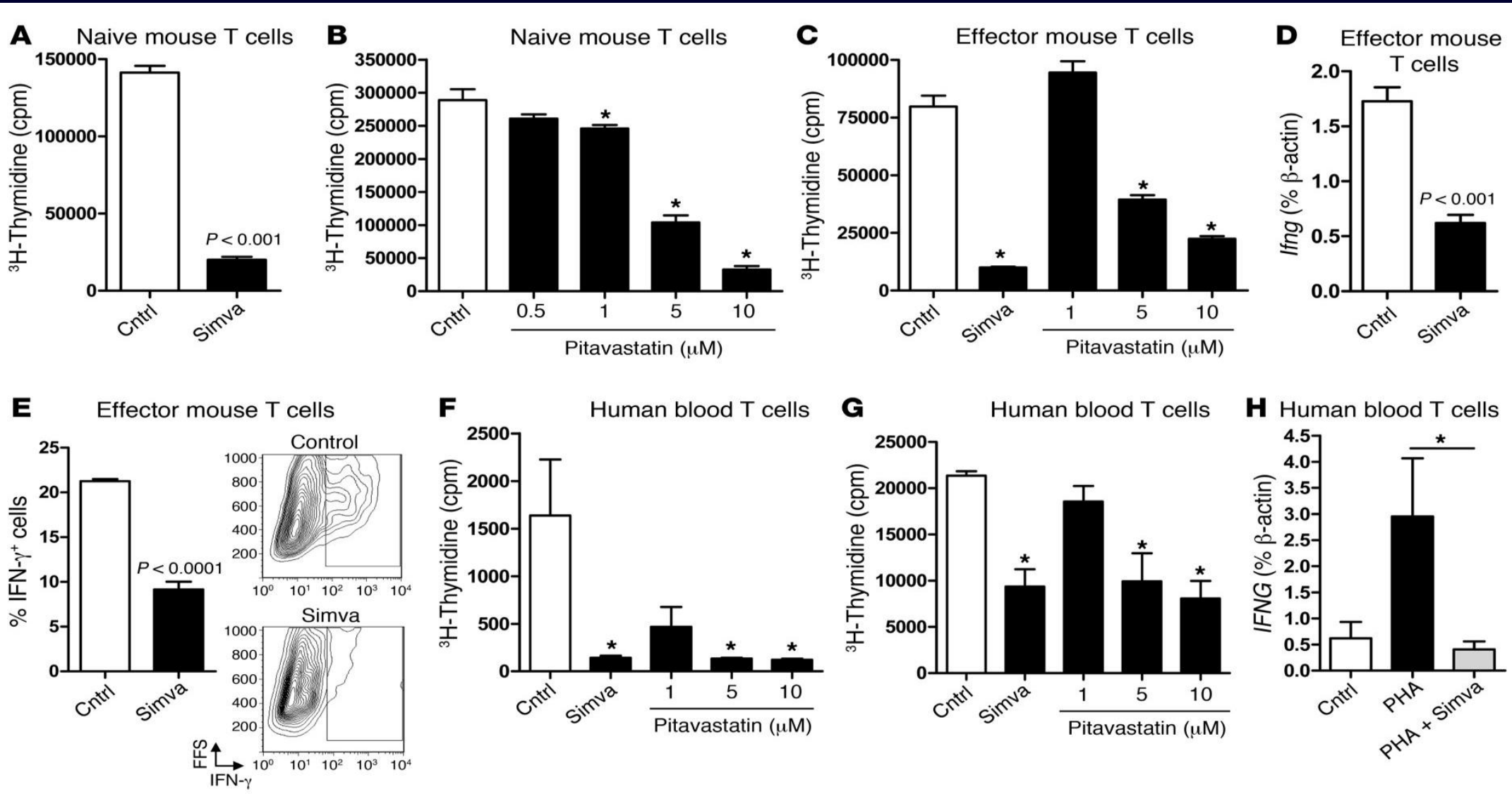
The transcription factor kruppel-like factor 2 (KLF2) is required for the quiescent and migratory properties of naive T cells. Statins, a class of HMG-CoA reductase inhibitors, display pleiotropic immunomodulatory effects that are independent of their lipid-lowering capacity and may be beneficial as therapeutic agents for T cell–mediated inflammatory diseases. Statins upregulate KLF2 expression in endothelial cells, and this activity is associated with an antiinflammatory phenotype. We therefore hypothesized that the immunomodulatory effects of statins are due, in part, to their direct effects on T cell *KLF2* gene expression. Here we report that lipophilic statin treatment of mouse and human T cells increased expression of KLF2 through a HMG-CoA/prenylation–dependent pathway. Statins also diminished T cell proliferation and IFN-γ expression. shRNA blockade of *KLF2* expression in human T cells increased IFN-γ expression and prevented statin-induced IFN-γ reduction. In a mouse model of myocarditis induced by heart antigen–specific $CD8^+$ T cells, both statin treatment of the T cells and retrovirally mediated overexpression of KLF2 in the T cells had similar ameliorating effects on disease induction. We conclude that statins reduce inflammatory functions and pathogenic activity of T cells through KLF2-dependent mechanisms, and this pathway may be a potential therapeutic target for cardiovascular diseases.

The Journal of Clinical Investigation June 2010

Statins reduce T cell proliferation and cytokine expression in vitro



Bu DX, Tarrio M, Grabie N, et al. Statin-induced Krüppel-like factor 2 expression in human and mouse T cells reduces inflammatory and pathogenic responses. J Clin Invest 2010;120:1961-70.

Do Statins' Benefits Reach Beyond Lowering LDL?

- LDL-Lowering effect
- "Pleiotropic" effects

Both mechanisms contribute to statins' clinical benefits