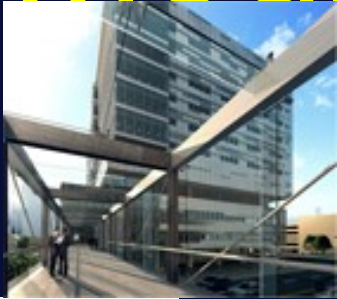


# Biomarkers and Personalized Medicine Novel Approaches and Clinical Utility

Peter Libby

Brigham & Women's Hospital  
Harvard Medical School



## CMOD Canada II

Ottawa

May 17, 2010



A feature article from...

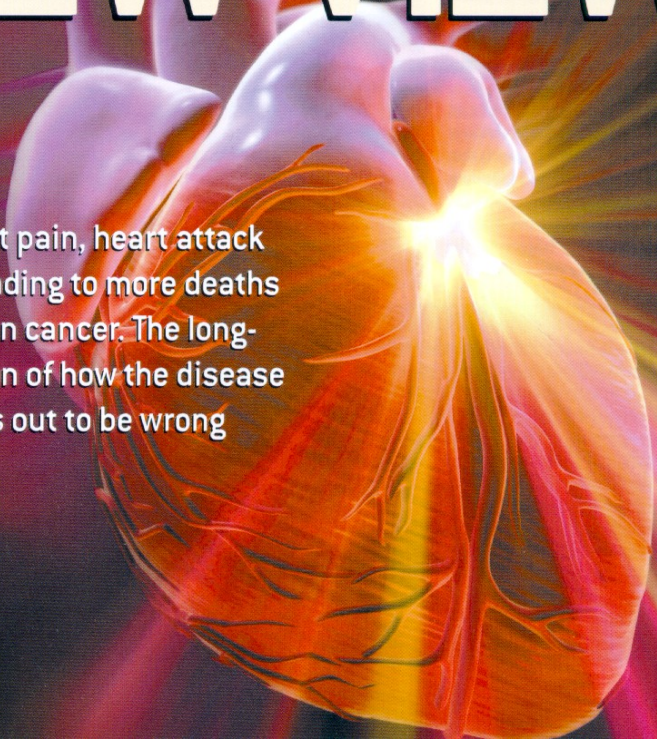
MAY 2002

# SCIENTIFIC AMERICAN

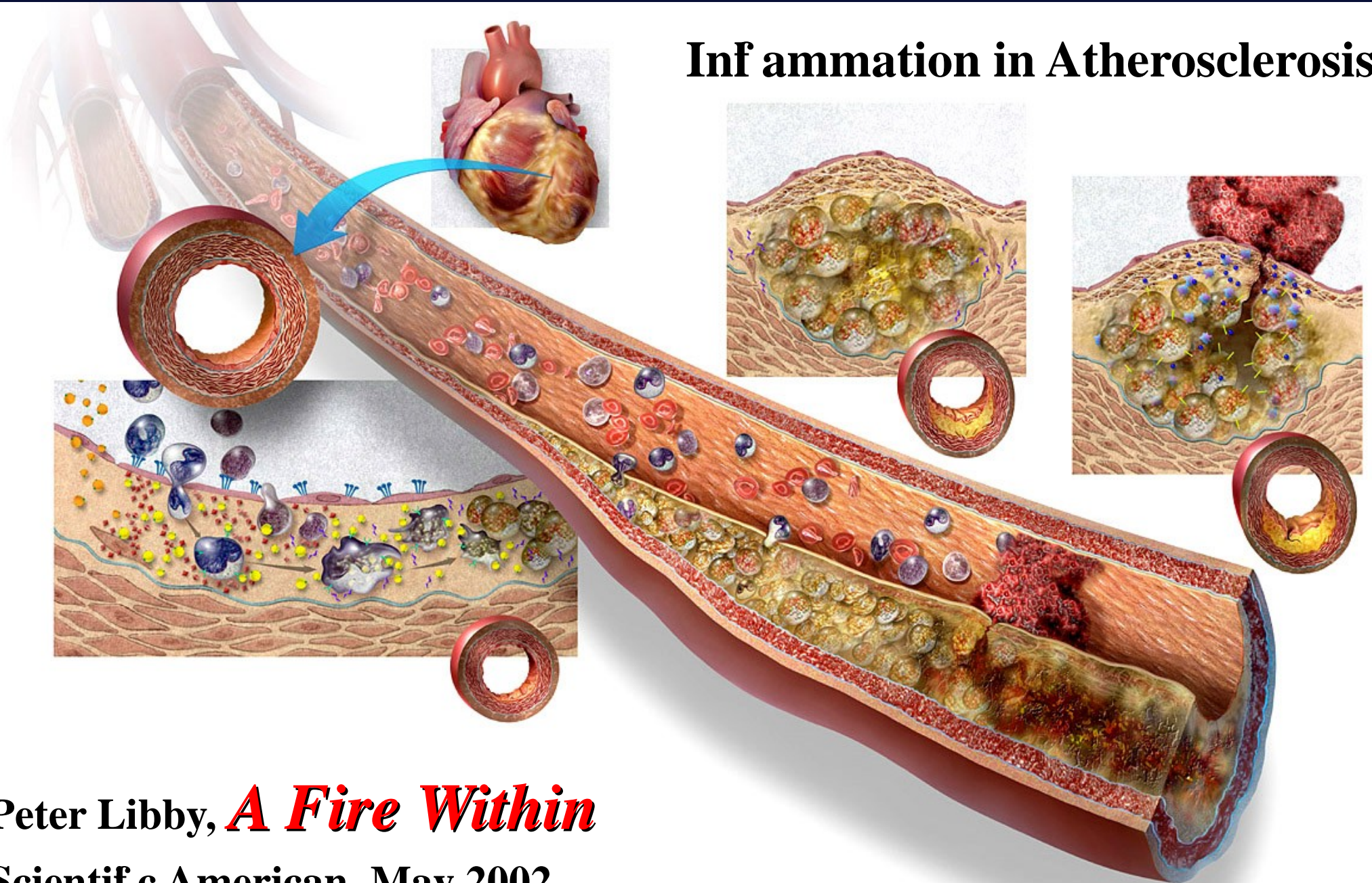
## ATHEROSCLEROSIS: THE NEW VIEW

It causes chest pain, heart attack and stroke, leading to more deaths every year than cancer. The long-held conception of how the disease develops turns out to be wrong

By Peter Libby

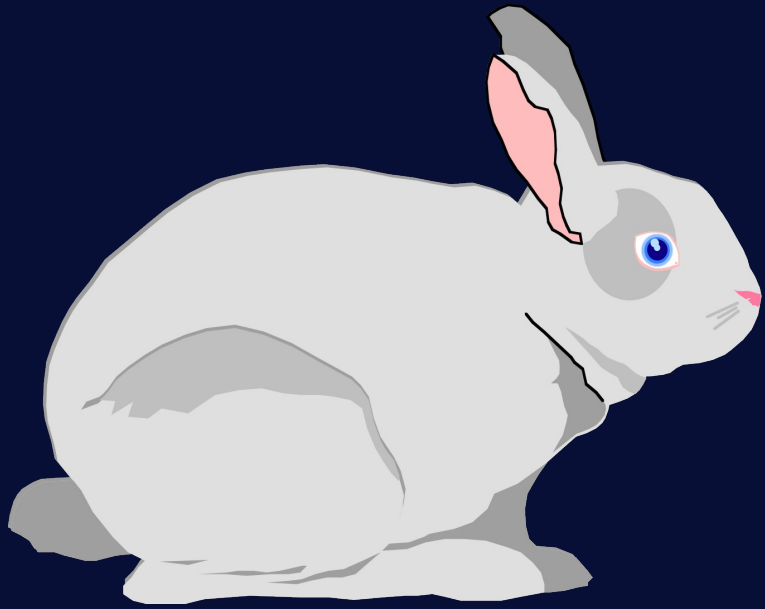


# Inflammation in Atherosclerosis

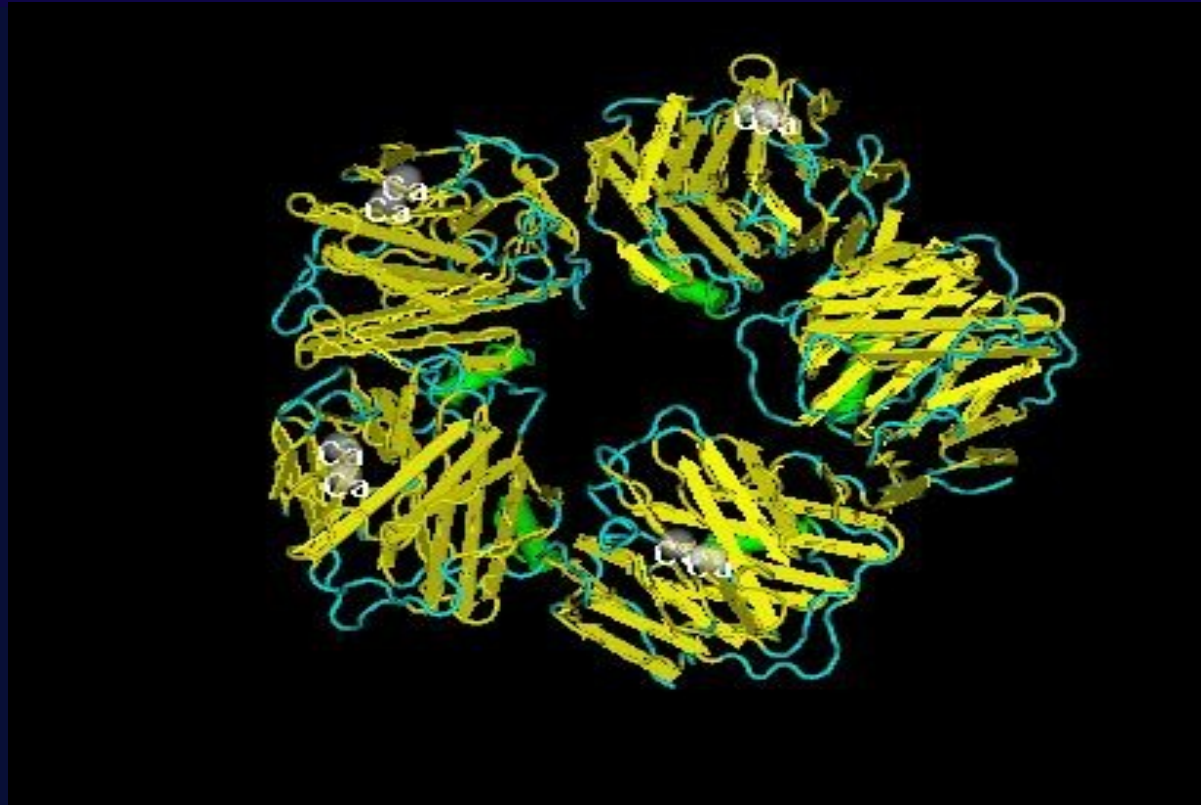


Peter Libby, *A Fire Within*

Scientific American May 2002



# Can we use inflammatory markers in the clinic?

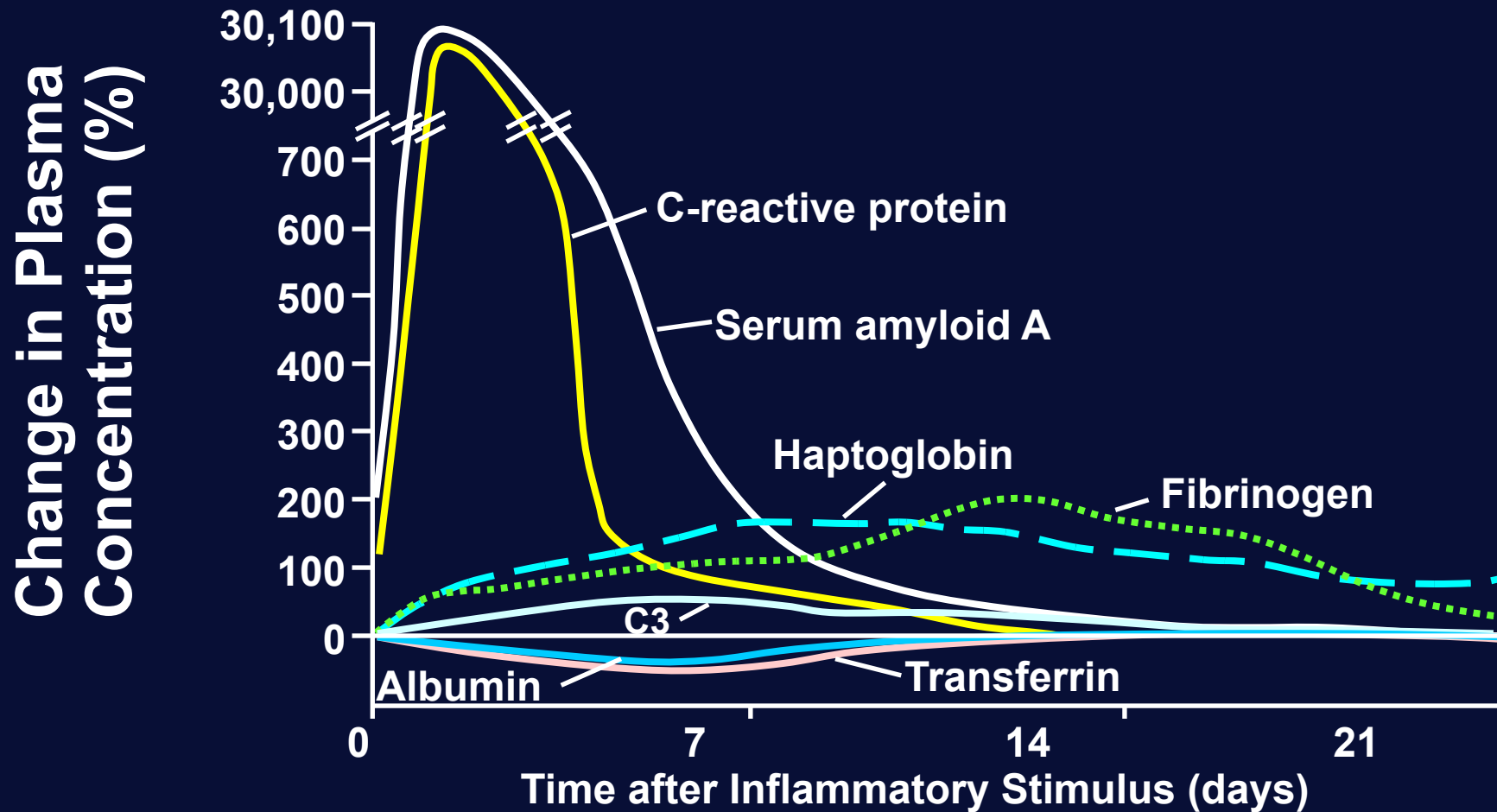


**C-reactive protein: CRP**

# Why CRP?

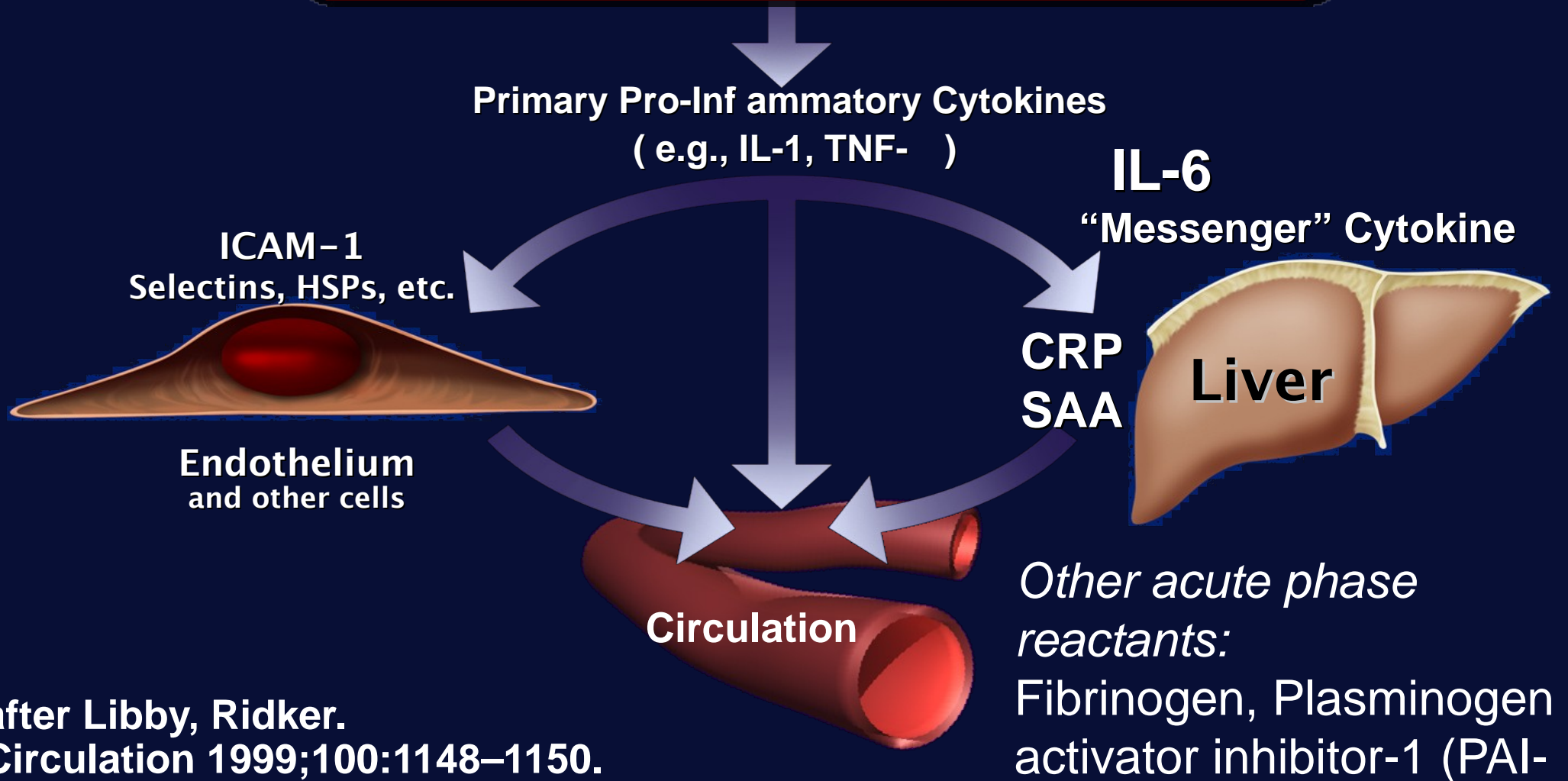
- ✧ **Stable chemically**
- ✧ **Reliable, standardized, convenient, and inexpensive assay**
- ✧ **Long half-life (ca. 24 h)**
- ✧ **No diurnal variation**
- ✧ **Levels fluctuate little in the well**
- ✧ **High dynamic range**

# Change in Acute-Phase Reactants After a Moderate Inflammatory Stimulus



# Inflammation Pathways in Atherogenesis

## Pro-Inflammatory Risk Factors



after Libby, Ridker.  
Circulation 1999;100:1148-1150.



# C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis

*The Emerging Risk Factors Collaboration\**

## Summary

**Lancet** 2010; 375: 132–40

Published Online

December 22, 2009

DOI:10.1016/S0140-

**Background** Associations of C-reactive protein (CRP) concentration with risk of major diseases can best be assessed by long-term prospective follow-up of large numbers of people. We assessed the associations of CRP concentration with risk of vascular and non-vascular outcomes under different circumstances.

**Methods** We meta-analysed individual records of 160 309 people without a history of vascular disease (ie, 1.31 million person-years at risk, 27 769 fatal or non-fatal disease outcomes) from 54 long-term prospective studies. Within-study regression analyses were adjusted for within-person variation in risk factor levels.

**Results** Log<sub>e</sub> CRP concentration was linearly associated with several conventional risk factors and inflammatory markers, and nearly log-linearly with the risk of ischaemic vascular disease and non-vascular mortality. Risk ratios (RRs) for coronary heart disease per 1-SD higher log<sub>e</sub> CRP concentration (three-fold higher) were 1.63 (95% CI 1.51–1.76) when initially adjusted for age and sex only, and 1.37 (1.27–1.48) when adjusted further for conventional risk factors; 1.44 (1.32–1.57) and 1.27 (1.15–1.40) for ischaemic stroke; 1.71 (1.53–1.91) and 1.55 (1.37–1.76) for vascular mortality; and 1.55 (1.41–1.69) and 1.54 (1.40–1.68) for non-vascular mortality. RRs were largely unchanged after exclusion of smokers or initial follow-up. After further adjustment for fibrinogen, the corresponding RRs were 1.23 (1.07–1.42) for coronary heart disease; 1.32 (1.18–1.49) for ischaemic stroke; 1.34 (1.18–1.52) for vascular mortality; and 1.34 (1.20–1.50) for non-vascular mortality.

**Interpretation** CRP concentration has continuous associations with the risk of coronary heart disease, ischaemic stroke, vascular mortality, and death from several cancers and lung disease that are each of broadly similar size. The relevance of CRP to such a range of disorders is unclear. Associations with ischaemic vascular disease depend considerably on conventional risk factors and other markers of inflammation.

emerging risk factors

Collaboration Coordinating

Centre, Department of Public

Health and Primary Care,

University of Cambridge,

Strangeways Research Laboratory,

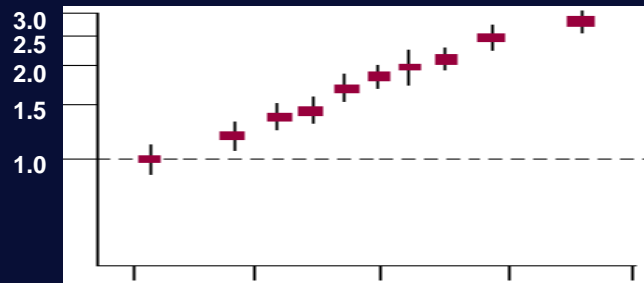
Cambridge CB1 8RN, UK

erfc@phpc.cam.ac.uk

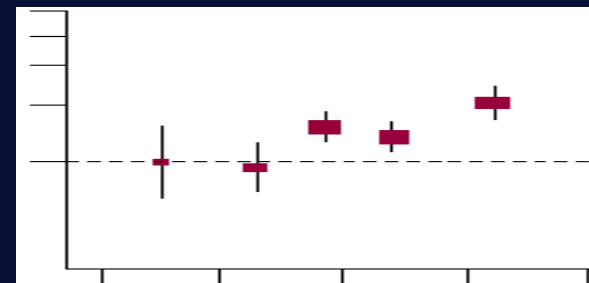
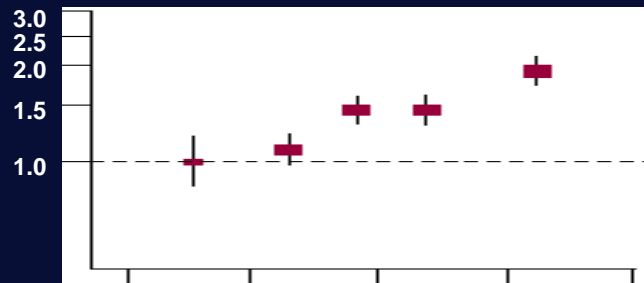
# C-reactive protein concentration and risk of cardiovascular events : 2010

Risk ratio (95% CI)

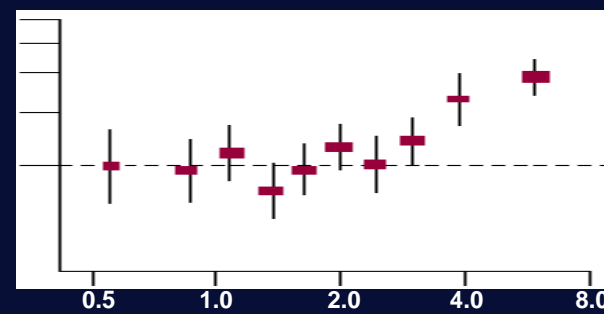
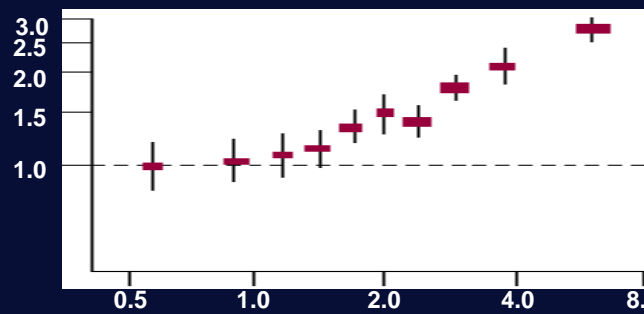
## Coronary Heart Disease



## Ischaemic Stroke



## All Vascular Deaths



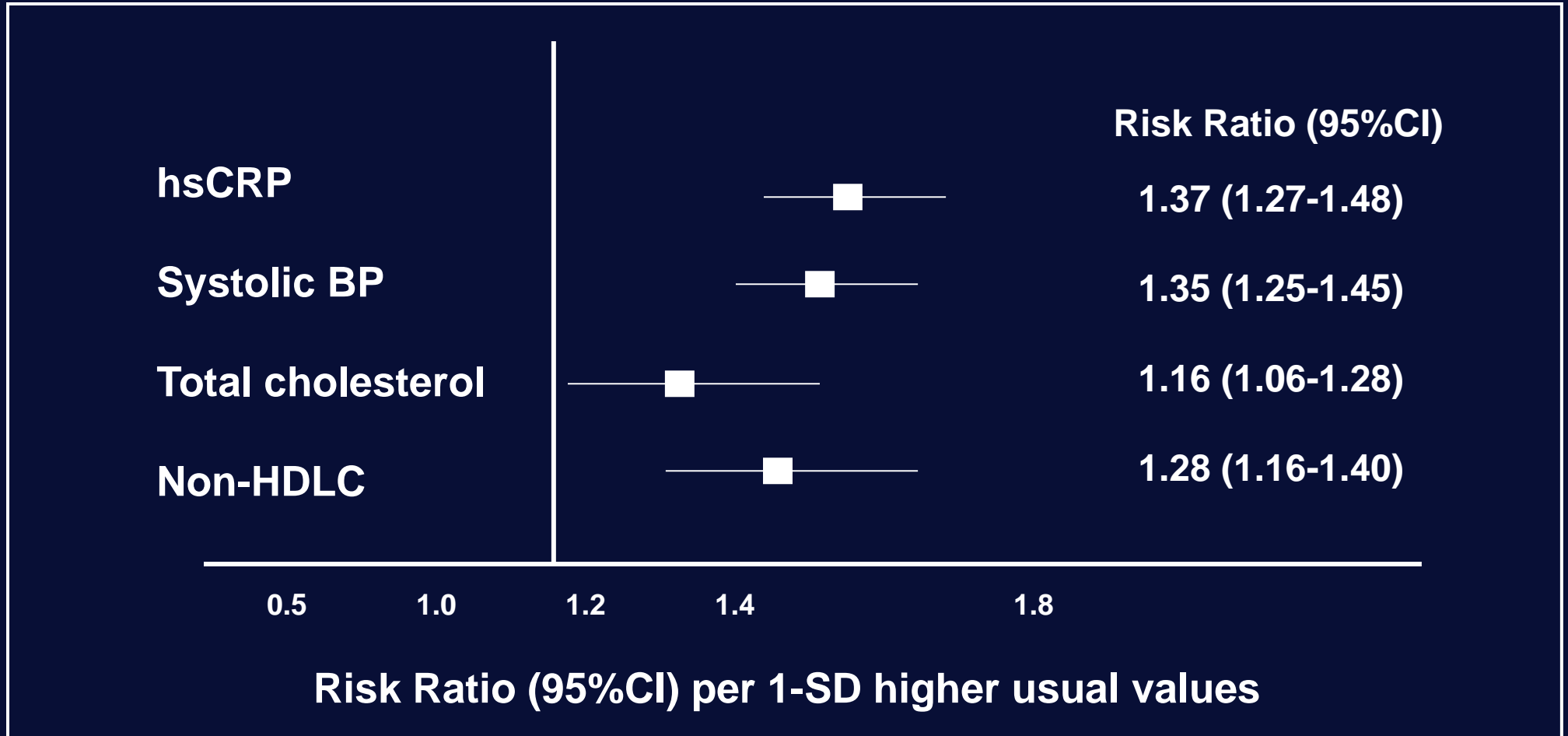
hsCRP concentration (mg/L)

Age, gender adjusted

Fully adjusted

# C-reactive protein concentration and risk of cardiovascular events : 2010

## *Direct comparison of hsCRP, systolic blood pressure, total cholesterol, and non-HDLC*



Adjusted for age, gender, smoking, diabetes, BMI, BP, triglycerides, alcohol, lipid levels, and hsCRP

Emerging Risk Factor Collaborators, Lancet Jan 2010

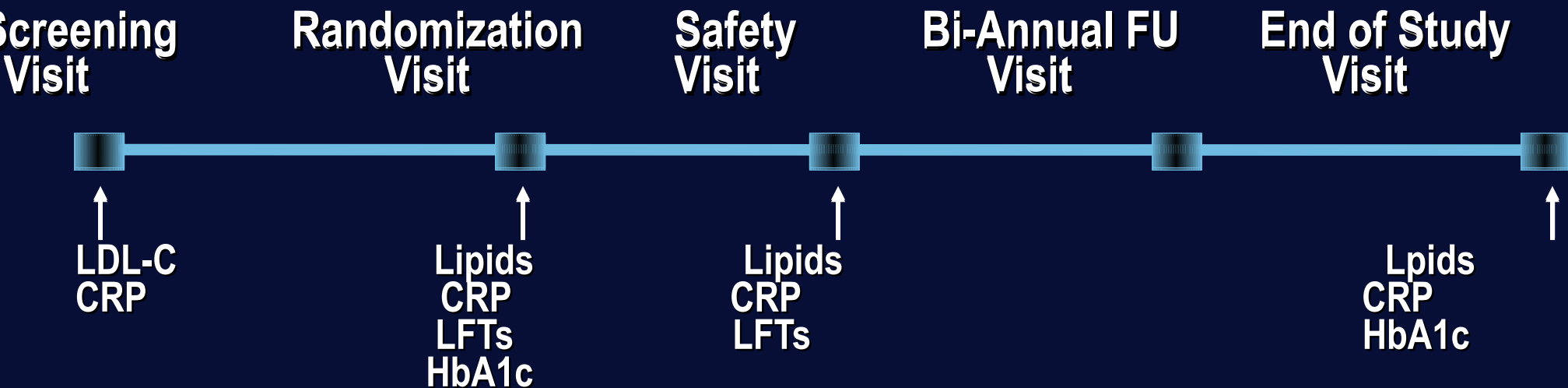
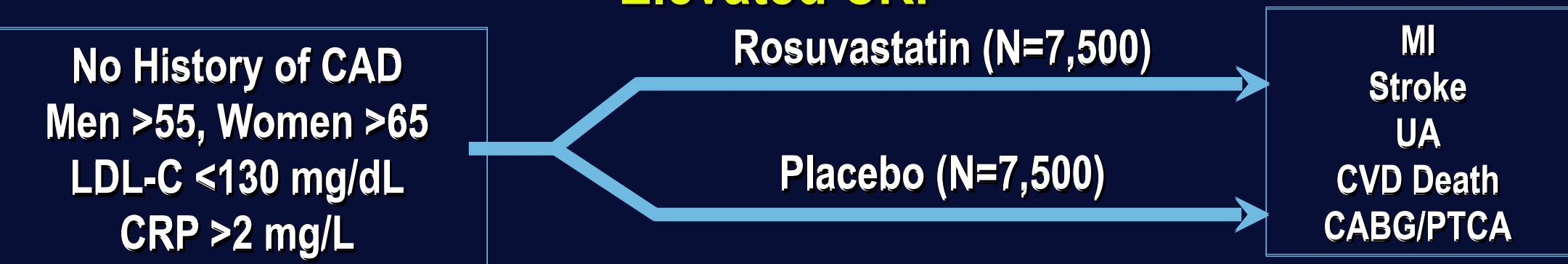
# Clinical utility of inflammatory markers

- ♥ Useful for screening?
- ♥ Target for therapy?
- ♥ *Guide for therapy?*

# Should we use inflammatory markers to guide therapy?

Until recently there was no evidence that CRP-guided therapy improves outcomes.

# JUPITER: Rosuvastatin in the Primary Prevention of Cardiovascular Events in Individuals with Average LDL-C and Elevated CRP



LFTs = liver function tests

# JUPITER

## Baseline Clinical Characteristics



	<b>Rosuvastatin (N = 8901)</b>	<b>Placebo (n = 8901)</b>
<b>Age, years (IQR)</b>	<b>66.0 (60.0-71.0)</b>	<b>66.0 (60.0-71.0)</b>
<b>Female, N (%)</b>	<b>3,426 (38.5)</b>	<b>3,375 (37.9)</b>
<b>Ethnicity, N (%)</b>		
<i>Caucasian</i>	<b>6,358 (71.4)</b>	<b>6,325 (71.1)</b>
<i>Black</i>	<b>1,100 (12.4)</b>	<b>1,124 (12.6)</b>
<i>Hispanic</i>	<b>1,121 (12.6)</b>	<b>1,140 (12.8)</b>
<b>Blood pressure, mm (IQR)</b>		
<i>Systolic</i>	<b>134 (124-145)</b>	<b>134 (124-145)</b>
<i>Diastolic</i>	<b>80 (75-87)</b>	<b>80 (75-87)</b>
<b>Smoker, N (%)</b>	<b>1,400 (15.7)</b>	<b>1,420 (16.0)</b>
<b>Family History, N (%)</b>	<b>997 (11.2)</b>	<b>1,048 (11.8)</b>
<b>Metabolic Syndrome, N (%)</b>	<b>3,652 (41.0)</b>	<b>3,723 (41.8)</b>
<b>Aspirin Use, N (%)</b>	<b>1,481 (16.6)</b>	<b>1,477 (16.6)</b>

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



31 March 2008

## Crestor Outcomes Study JUPITER Closes Early Due To Unequivocal Evidence Of Benefit

AstraZeneca today announced it has decided to stop the CRESTOR JUPITER clinical study early based on a recommendation from an Independent Data Monitoring Board and the JUPITER Steering Committee, which met on March 29, 2008. The study will be stopped early because there is unequivocal evidence of a reduction in cardiovascular morbidity and mortality amongst patients who received CRESTOR when compared to placebo.

JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) was designed to determine if treating patients with no evidence of pre-existing cardiovascular disease and low to normal LDL-C but elevated C-reactive protein (CRP) with CRESTOR 20mg once daily would reduce major cardiovascular events. CRP is a recognized marker of inflammation and is associated with an increased risk of atherosclerotic cardiovascular events.

# *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

NOVEMBER 20, 2008

VOL. 359 NO. 21

## Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein

Paul M Ridker, M.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D.,  
Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D.,  
Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D.,  
James T. Willerson, M.D., and Robert J. Glynn, Sc.D., for the JUPITER Study Group\*

# JUPITER

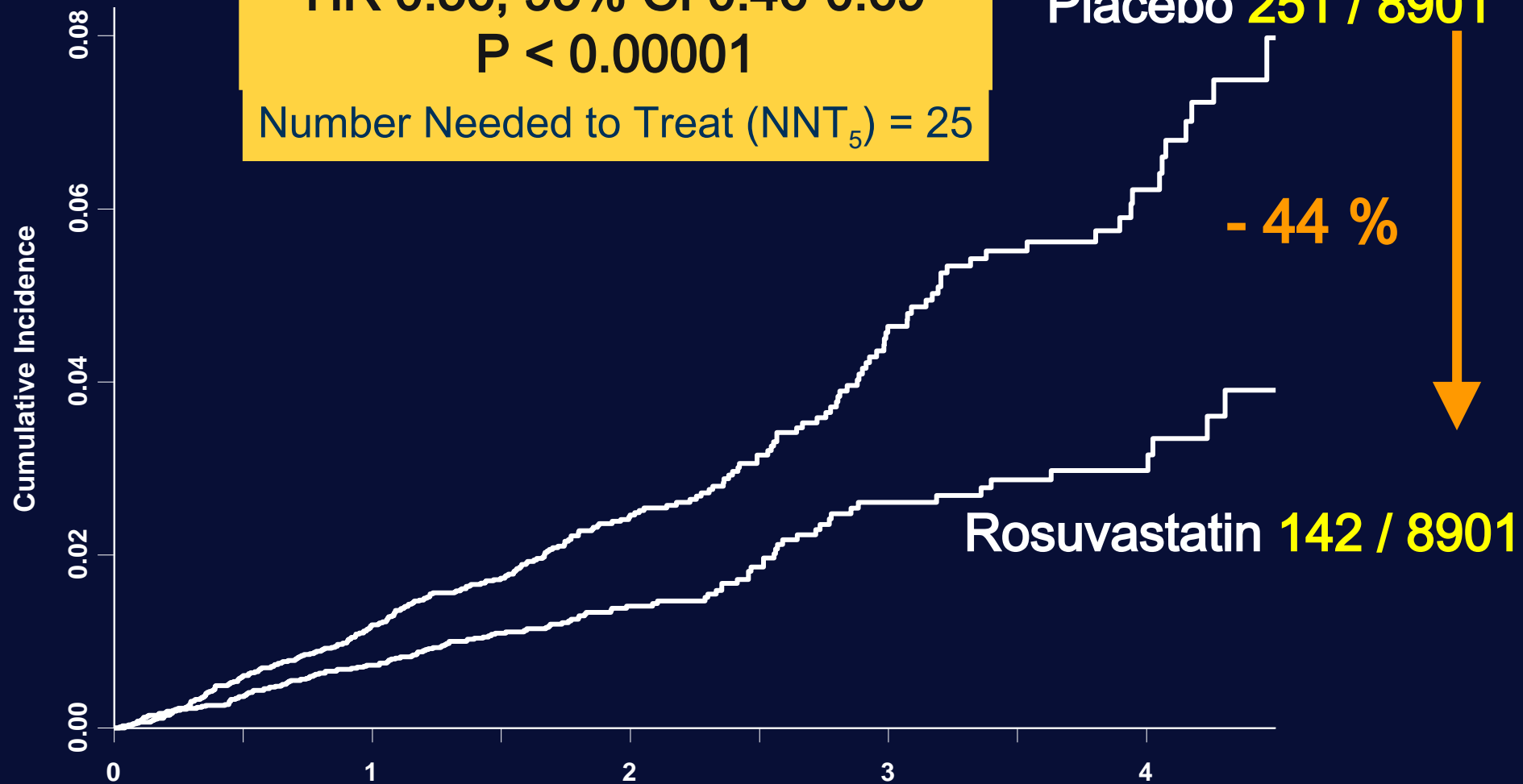


Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death

HR 0.56, 95% CI 0.46-0.69

P < 0.00001

Number Needed to Treat (NNT<sub>5</sub>) = 25

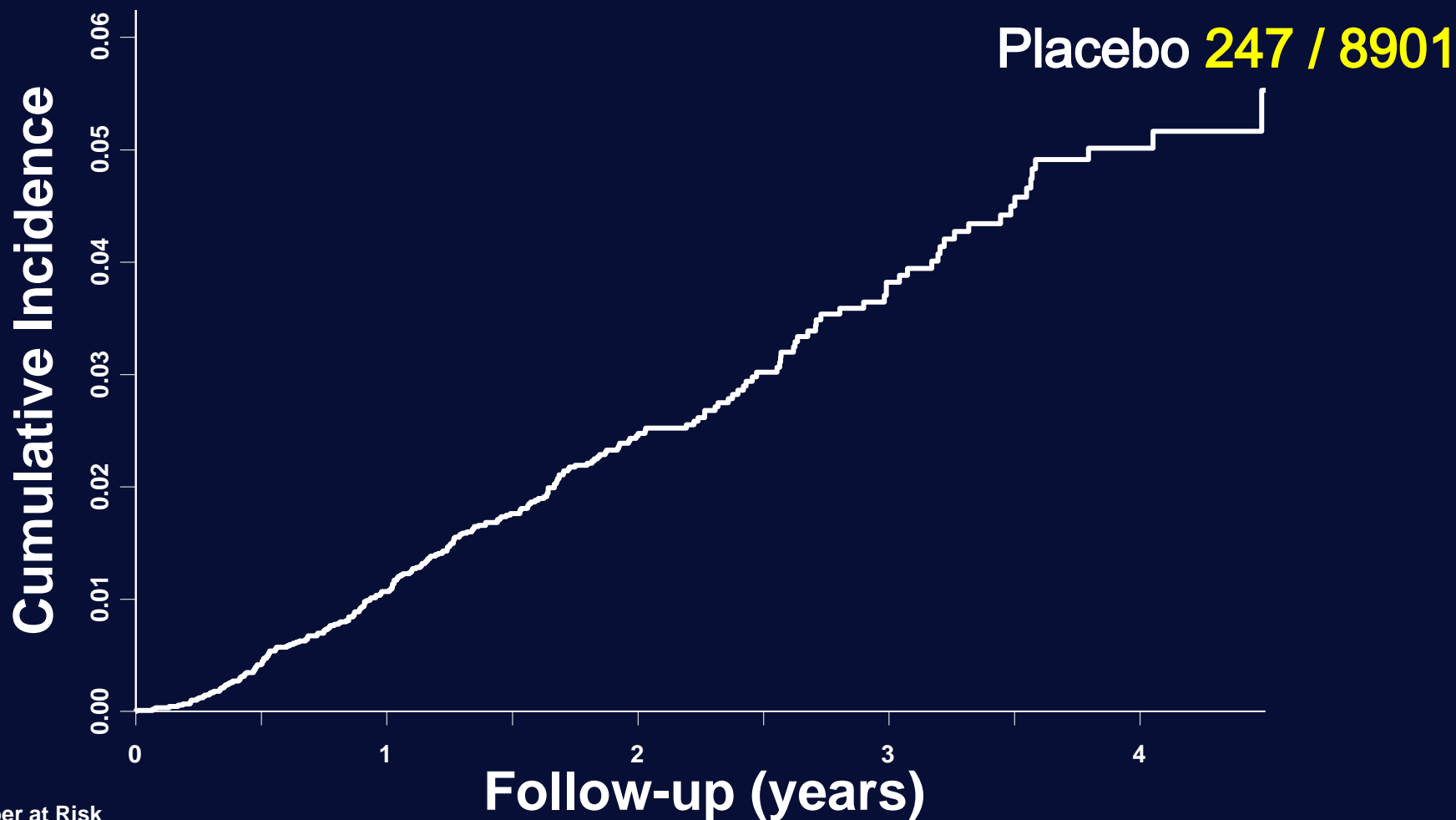


Number at Risk

	0	1	2	3	4	5
Rosuvastatin	8,901	8,631	8,412	6,540	3,893	1,958
Placebo	8,901	8,621	8,353	6,508	3,872	1,963

# JUPITER

## Secondary Endpoint – All Cause Mortality

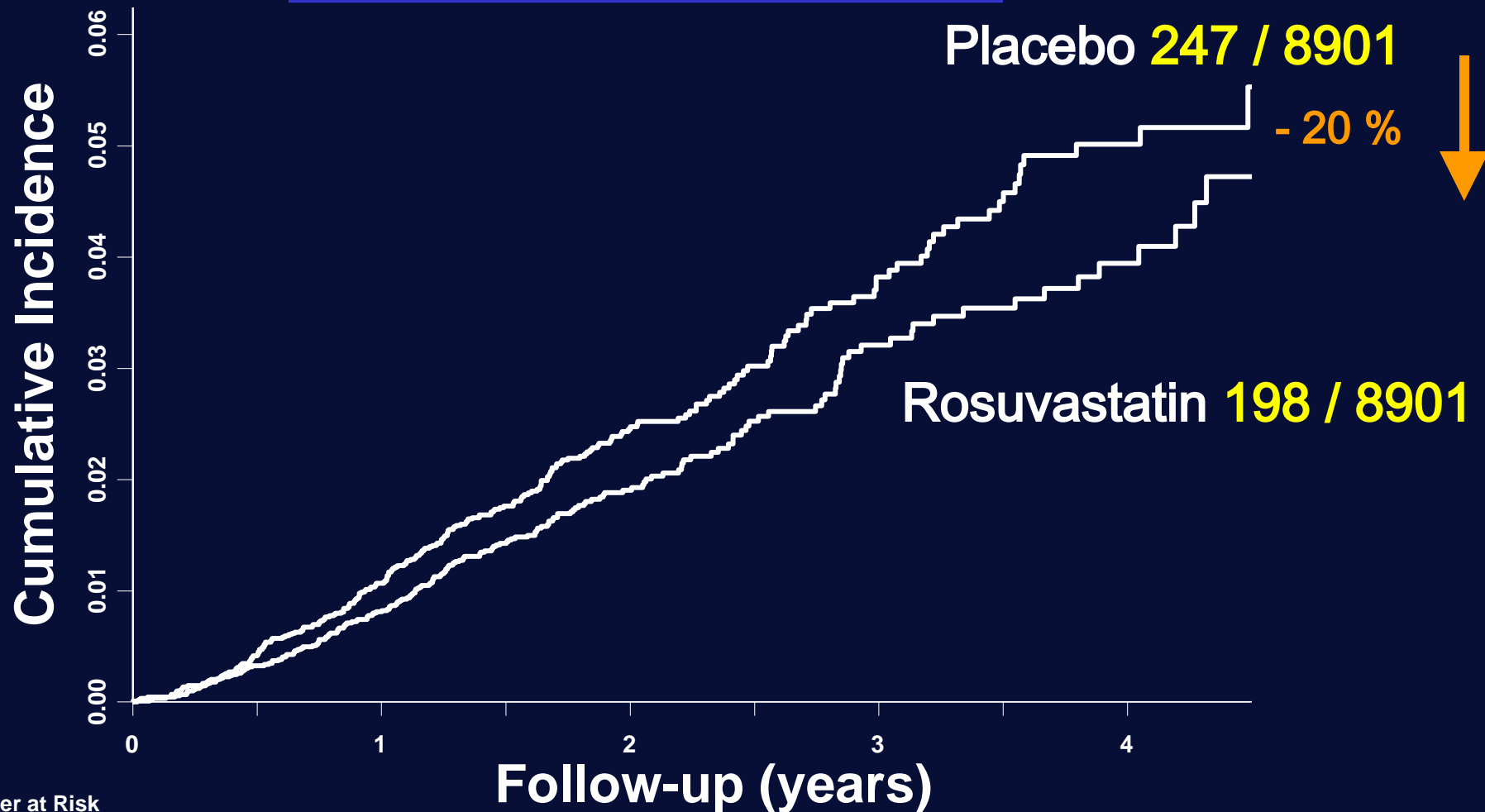


### Number at Risk

Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	683	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	684	246



HR 0.80, 95%CI 0.67-0.97  
P= 0.02



Number at Risk

Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	683	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	684	246



Event	Rosuvastatin	Placebo	P
<b>Any SAE</b>	1,352 (15.2)	1,337 (15.5)	0.60
<b>Muscle weakness</b>	1,421 (16.0)	1,375 (15.4)	0.34
<b>Myopathy</b>	10 (0.1)	9 (0.1)	0.82
<b>Rhabdomyolysis</b>	1 (0.01)*	0 (0.0)	--
<b>Incident Cancer</b>	298 (3.4)	314 (3.5)	0.51
<b>Cancer Deaths</b>	35 (0.4)	58 (0.7)	0.02
<b>Hemorrhagic stroke</b>	6 (0.1)	9 (0.1)	0.44
<b>GFR</b> (ml/min/1.73m <sup>2</sup> at 12 mth)	66.8 (59.1-76.5)	66.6 (58.8-76.2)	0.02
<b>ALT &gt; 3xULN</b>	23 (0.3)	17 (0.2)	0.34
<b>Fasting glucose</b> (24 mth)	98 (91-107)	98 (90-106)	0.12
<b>HbA1c</b> (% at 24 mth)	5.9 (5.7-6.1)	5.8 (5.6-6.1)	0.01
<b>Glucosuria</b> (12 mth)	36 (0.5)	32 (0.4)	0.64
<b>Incident Diabetes**</b>	270 (3.0)	216 (2.4)	0.01

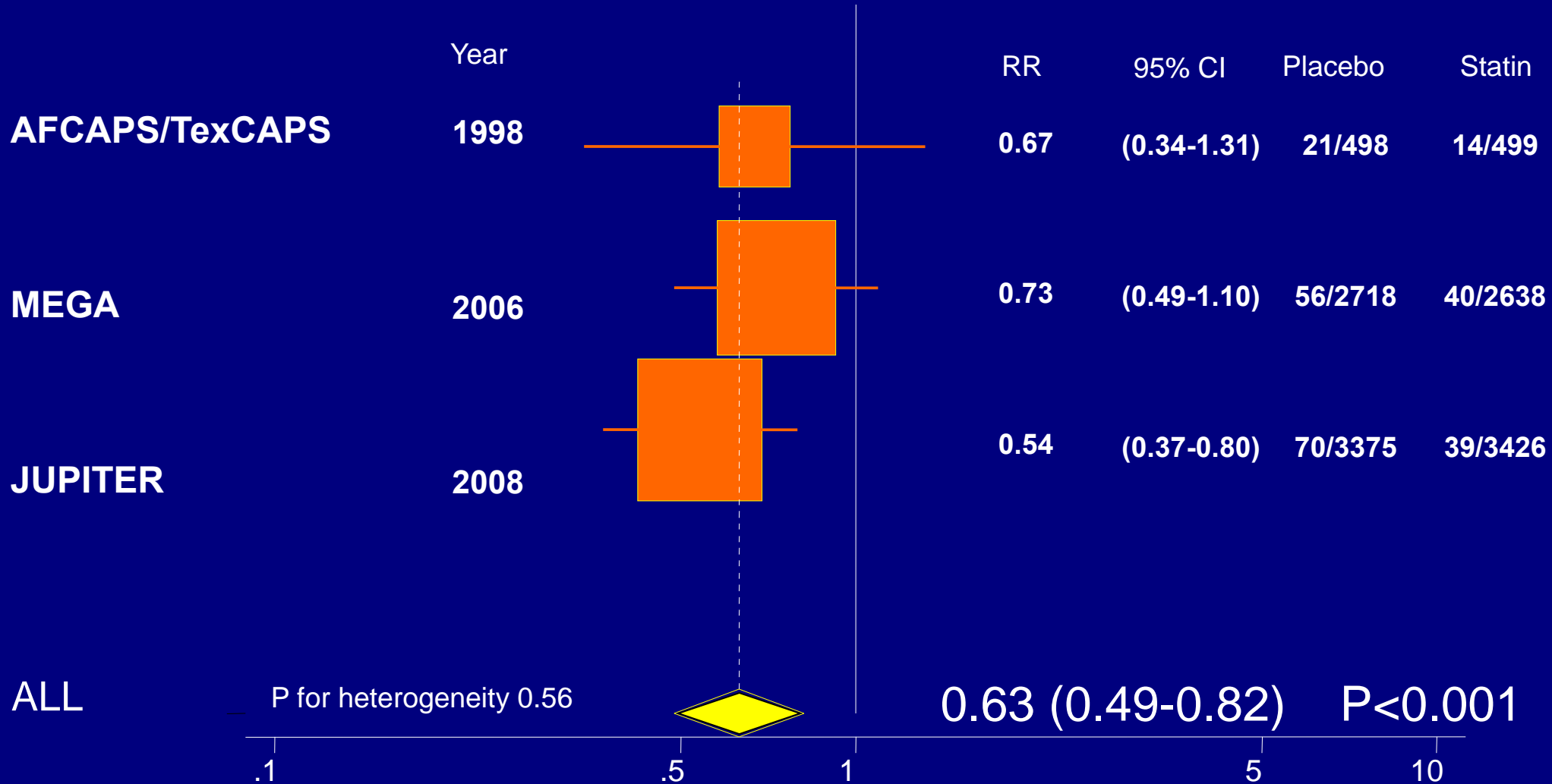
\*Occurred after trial completion, trauma induced.

\*\*Physician reported

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

# Meta-analysis of Exclusively Primary Prevention Statin Trials in Women

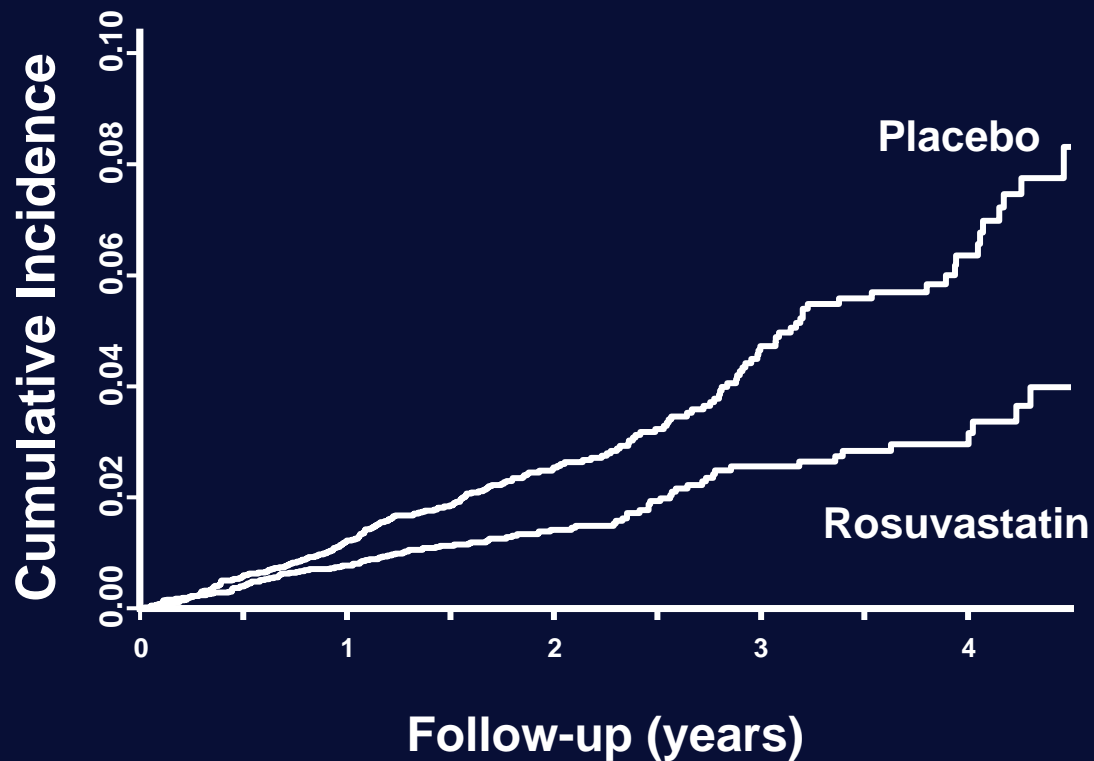
13 154 Women, 240 CVD events





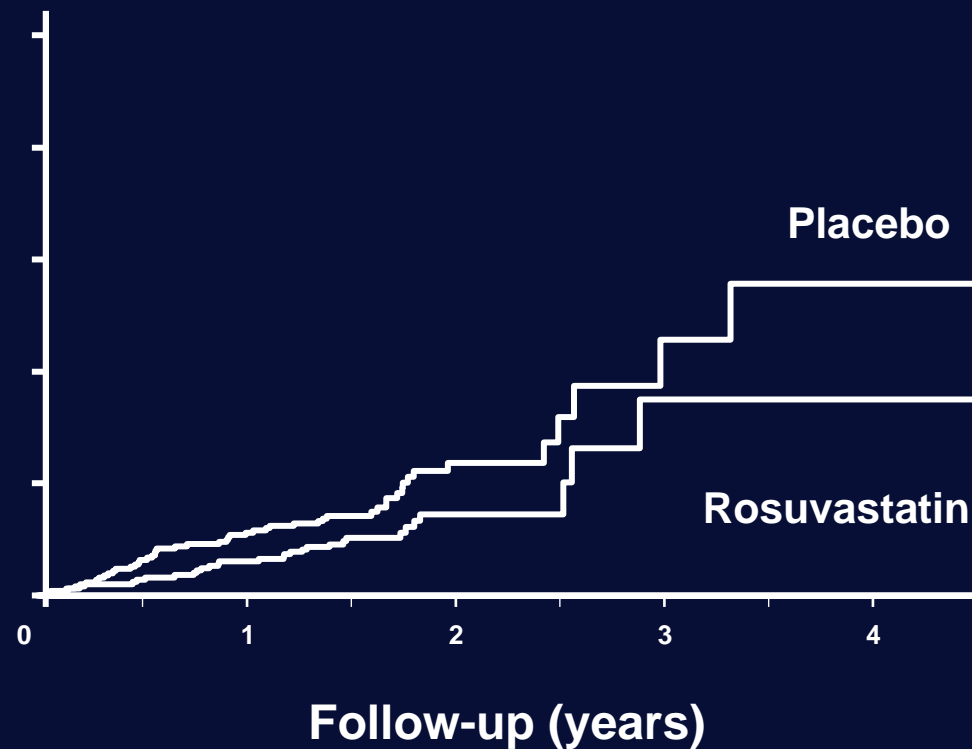
### Caucasian (N = 12,683)

HR 0.55, 95% CI 0.43-0.69  
P < 0.0001



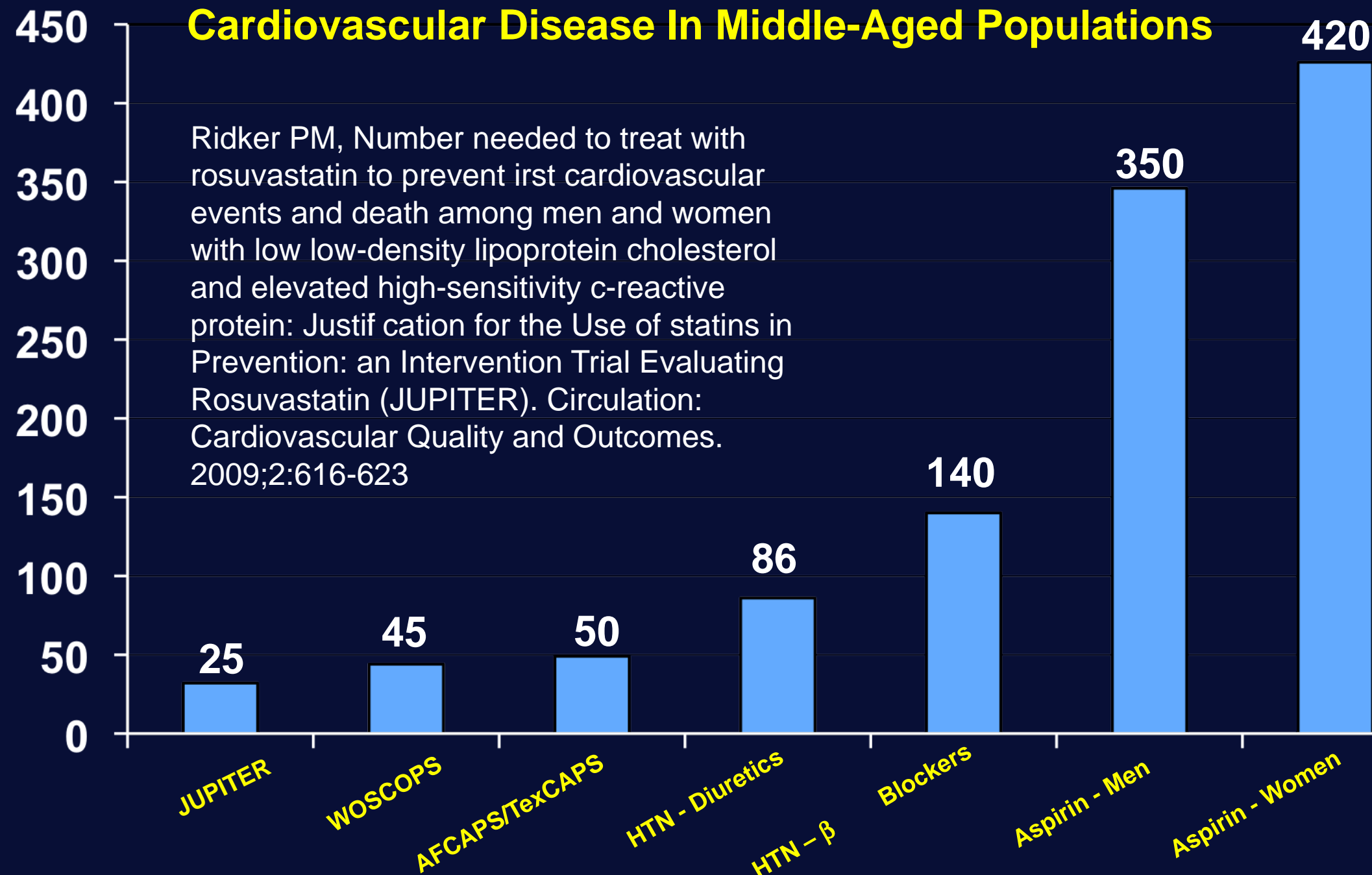
### Black, Hispanic, Other (N = 5,019)

HR 0.63, 95% CI 0.41-0.98  
P = 0.04



# Estimated 5-Year NNT Values for the Primary Prevention of Cardiovascular Disease In Middle-Aged Populations

Ridker PM, Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity c-reactive protein: Justification for the Use of statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER). *Circulation: Cardiovascular Quality and Outcomes.* 2009;2:616-623



# Information: Can it Change Minds to Save Hearts?

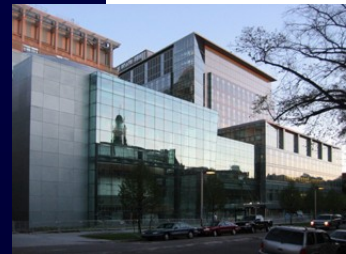
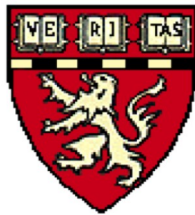
♥ Can the reduction to practice of information biology in atherothrombosis:

♥ *Change practice guidelines?*

♥ *Lead regulators to approve new indications?*



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# 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult – 2009 recommendations

Jacques Genest MD<sup>1</sup>, Ruth McPherson MD PhD<sup>2</sup>, Jiri Frohlich MD<sup>3</sup>, Todd Anderson MD<sup>4</sup>, Norm Campbell MD<sup>4</sup>, André Carpentier MD<sup>5</sup>, Patrick Couture MD<sup>6</sup>, Robert Dufour MD<sup>7</sup>, George Fodor MD<sup>2</sup>, Gordon A Francis MD<sup>3</sup>, Steven Grover MD<sup>1</sup>, Milan Gupta MD<sup>8</sup>, Robert A Hegele MD<sup>9</sup>, David C Lau MD<sup>10</sup>, Lawrence Leiter MD<sup>11</sup>, Gary F Lewis MD<sup>12</sup>, Eva Lonn MD<sup>13</sup>, GB John Mancini MD<sup>14</sup>, Dominic Ng MD PhD<sup>11</sup>, Glen J Pearson PharmD<sup>15</sup>, Allan Sniderman MD<sup>16</sup>, James A Stone MD PhD<sup>10</sup>, Ehud Ur MD<sup>14</sup>

Major Changes since 2006 Recommendations:

“hsCRP part of risk stratification in intermediate-risk subjects whose LDL-C does not already suggest treatment (men >50, women >60 years)”

Authors go further suggesting CRP <2 as a secondary treatment target

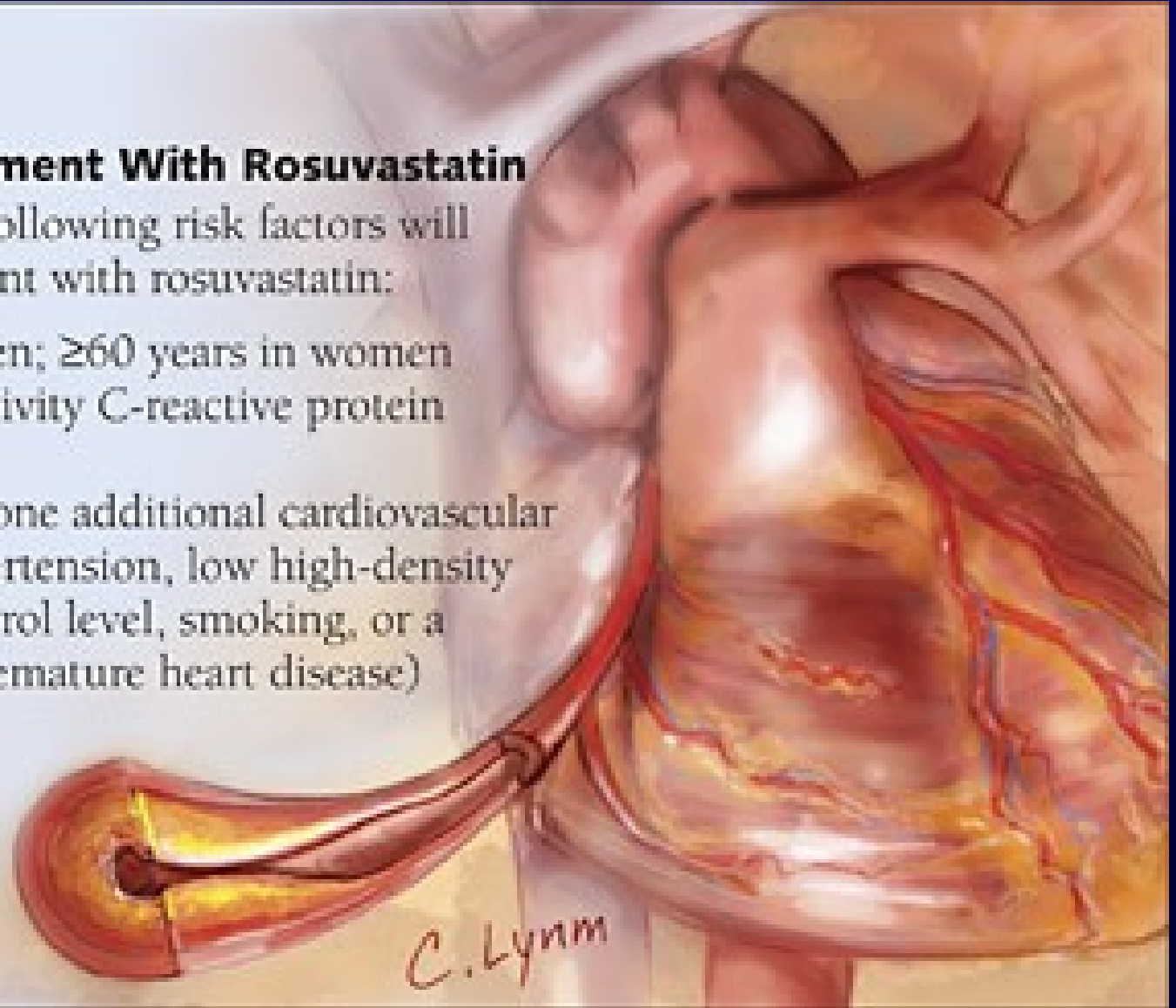
# The FDA Accepts Use of CRP for Targeting Therapy

## Eligibility for Treatment With Rosuvastatin

Individuals with the following risk factors will be eligible for treatment with rosuvastatin:

- Age  $\geq 50$  years in men;  $\geq 60$  years in women
- Elevated high-sensitivity C-reactive protein level ( $\geq 2$  mg/L)
- Presence of at least one additional cardiovascular risk factor (eg, hypertension, low high-density lipoprotein cholesterol level, smoking, or a family history of premature heart disease)

Source: US Food and Drug Administration



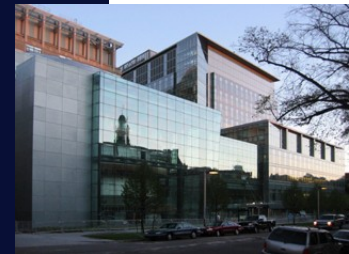
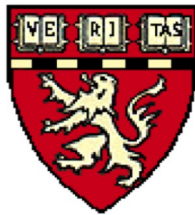
# Pathophysiology of Atherosclerosis: Key Points

♥ Inflammation drives all phases of atherosclerosis including initiation, progression, and complication

♥ Inflammation provides a common link between many risk factors for atherosclerosis and altered arterial biology



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# Pathophysiology of Atherosclerosis: Key Points

♥ Modification of risk factors can exert their clinical benefit by reducing inflammation

♥ Emerging evidence supports the use of inflammatory status to guide therapy that can reduce cardiovascular events in apparently well people



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