May 8th, 9:00 AM - 10:00 AM

Inflammation and Atherothrombosis: Where Have We Been? Where Are We Going? Why Perform the CIRT and CANTOS Trials? From Bench to Bedside to Population and Back: A Story of Clinical Translation

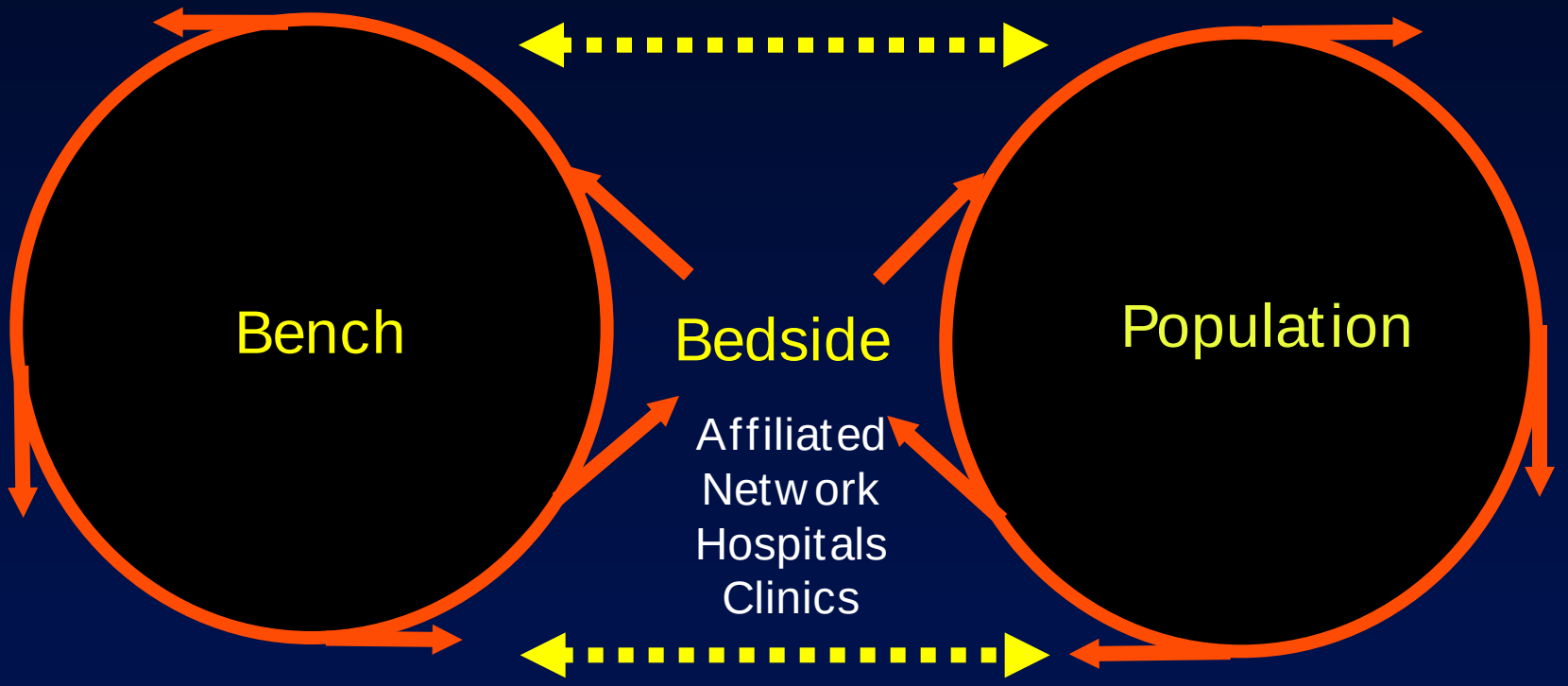
Paul M. Ridker
Harvard Medical School

Inflammation and Atherothrombosis: Where have we been? Where Are We Going? Why Perform the CIRT and CANTOS Trials?

From Bench to Bedside to Population and Back: A Story of Clinical Translation

Paul M Ridker, MD
Eugene Braunwald Professor of Medicine
Harvard Medical School
Director, Center for Cardiovascular Disease Prevention
Brigham and Women's Hospital, Boston MA

What is translational research? How does an integrated health care system support it?



T1, T2, T3

Dr Ridker has received investigator-initiated research support from the NHLBI, NCI, American Heart Association, Donald W Reynolds Foundation, Leduc Foundation, Doris Duke Charitable Foundation, AstraZeneca, Novartis, and SanofiAventis.

Dr Ridker has served as a consultant to Vascular Biogenics, Merck, ISIS, and Genzyme.

Dr Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital (BWH) that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to Seimens and AstraZeneca. Dr. Ridker and the BWH receive royalties on sales of the hsCRP test. However, neither Dr. Ridker nor the BWH receives any royalties attributable to sales of the hsCRP test used in connection with the CIRT or CANTOS trials.

CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

For More Information : (855) 437-9330

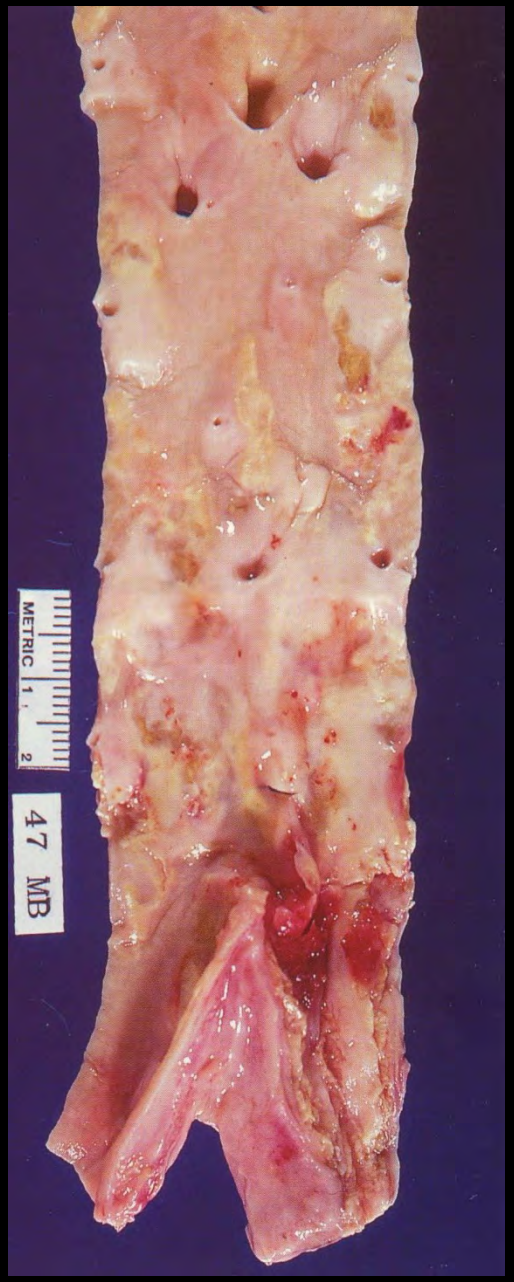
theCIRT.org theCANTOS.org

Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions

Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? 1995-2002

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? 2002-2008

Is there evidence that reducing inflammation per se will reduce vascular events? 2009 -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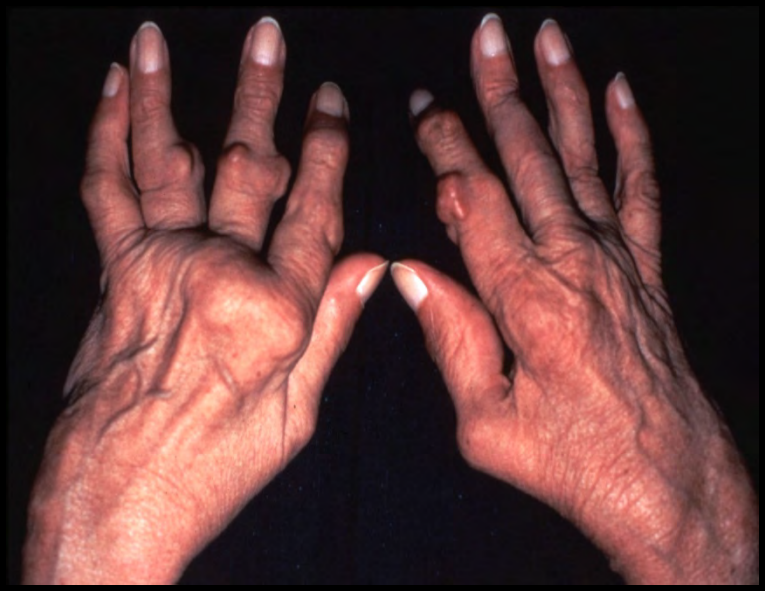
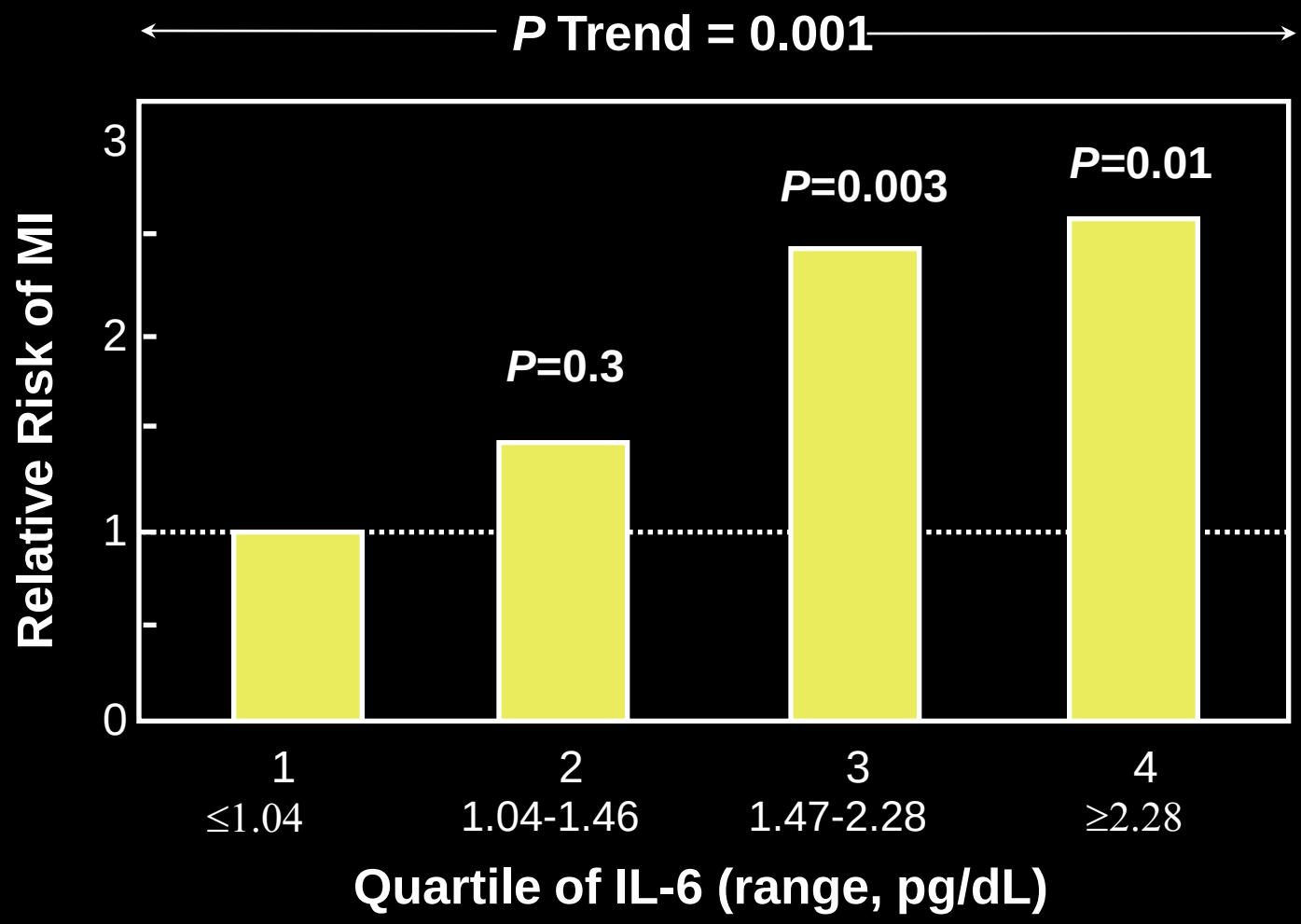
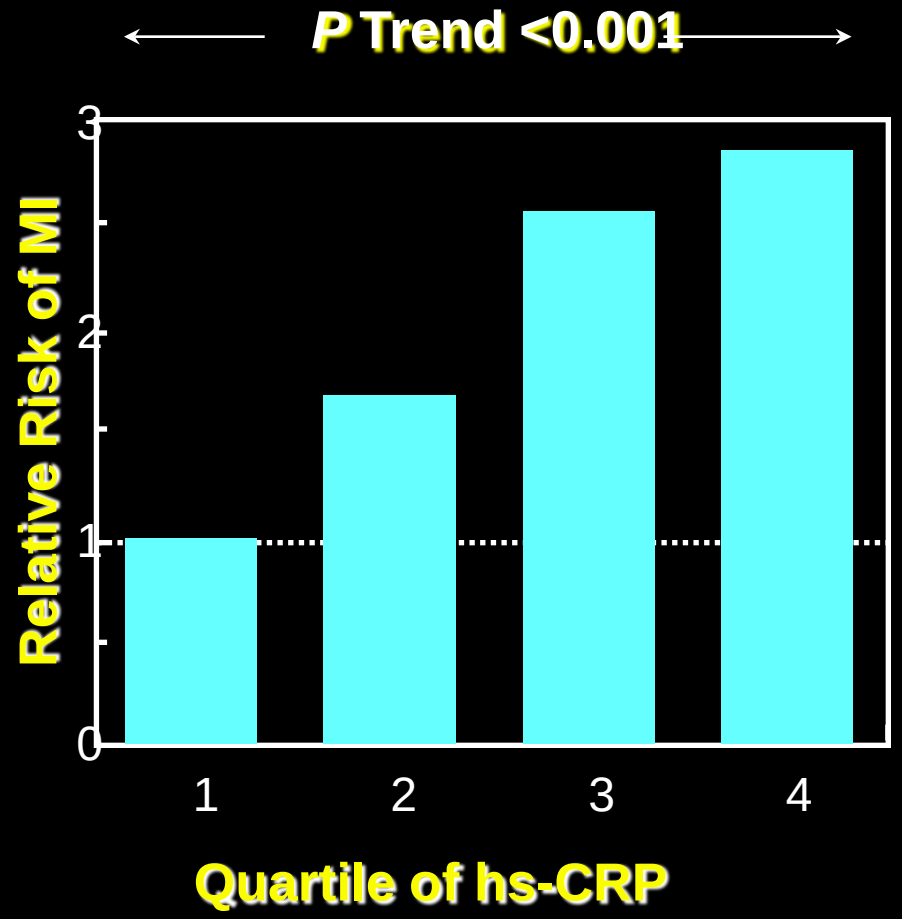


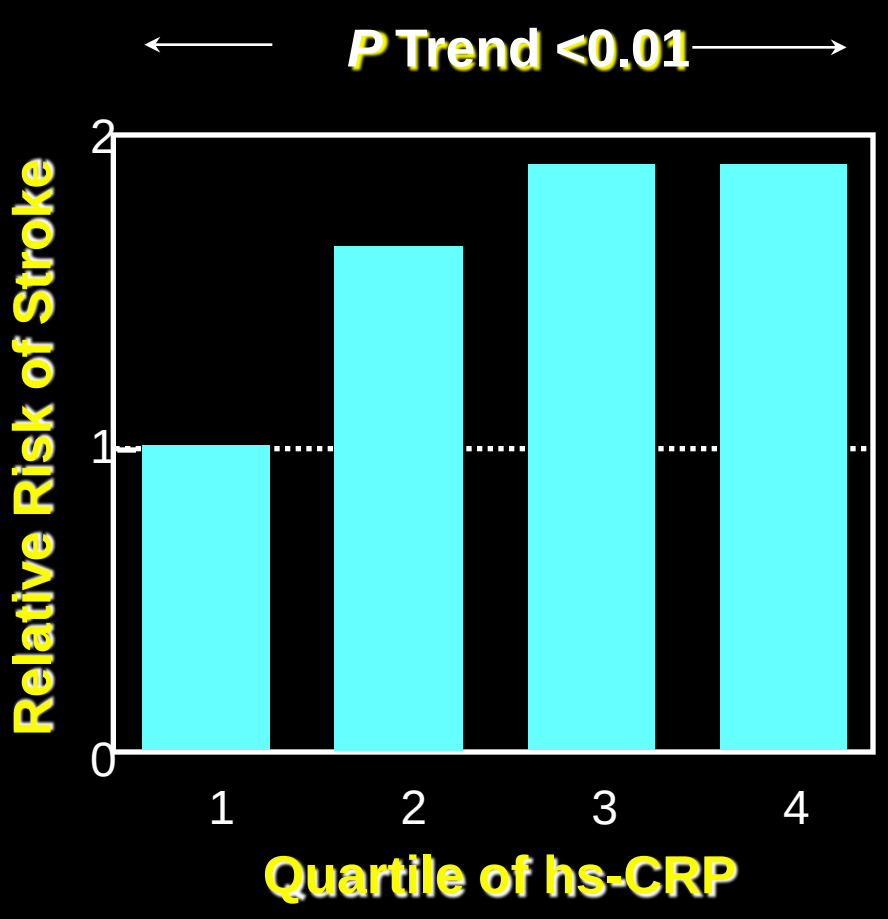
IL-6 and Risk of Future MI in Apparently Healthy Men



Ridker et al, Circulation 2000;101:1767-1772

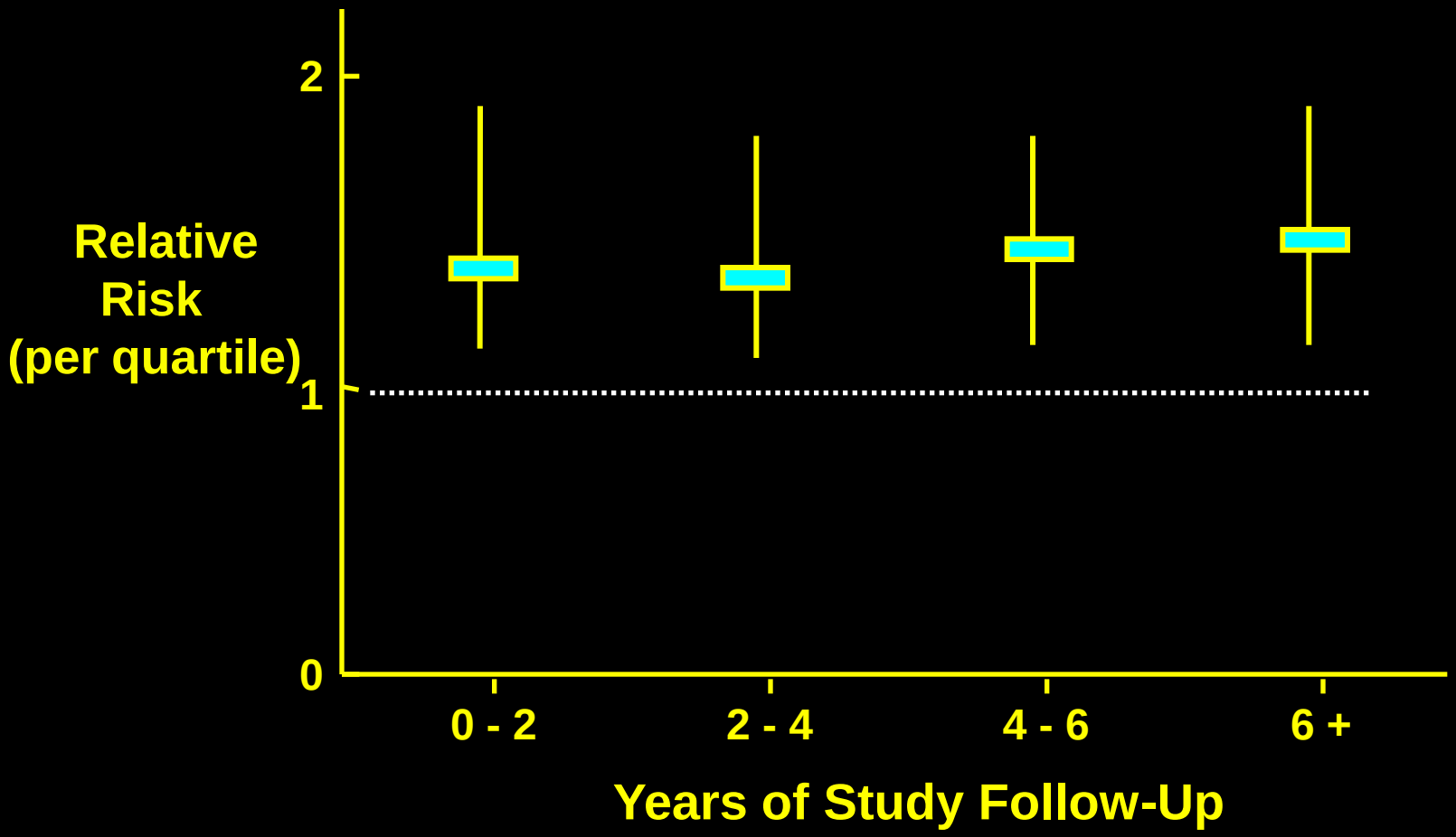
hsCRP and Risk of Future MI and CVA in Apparently Healthy Men





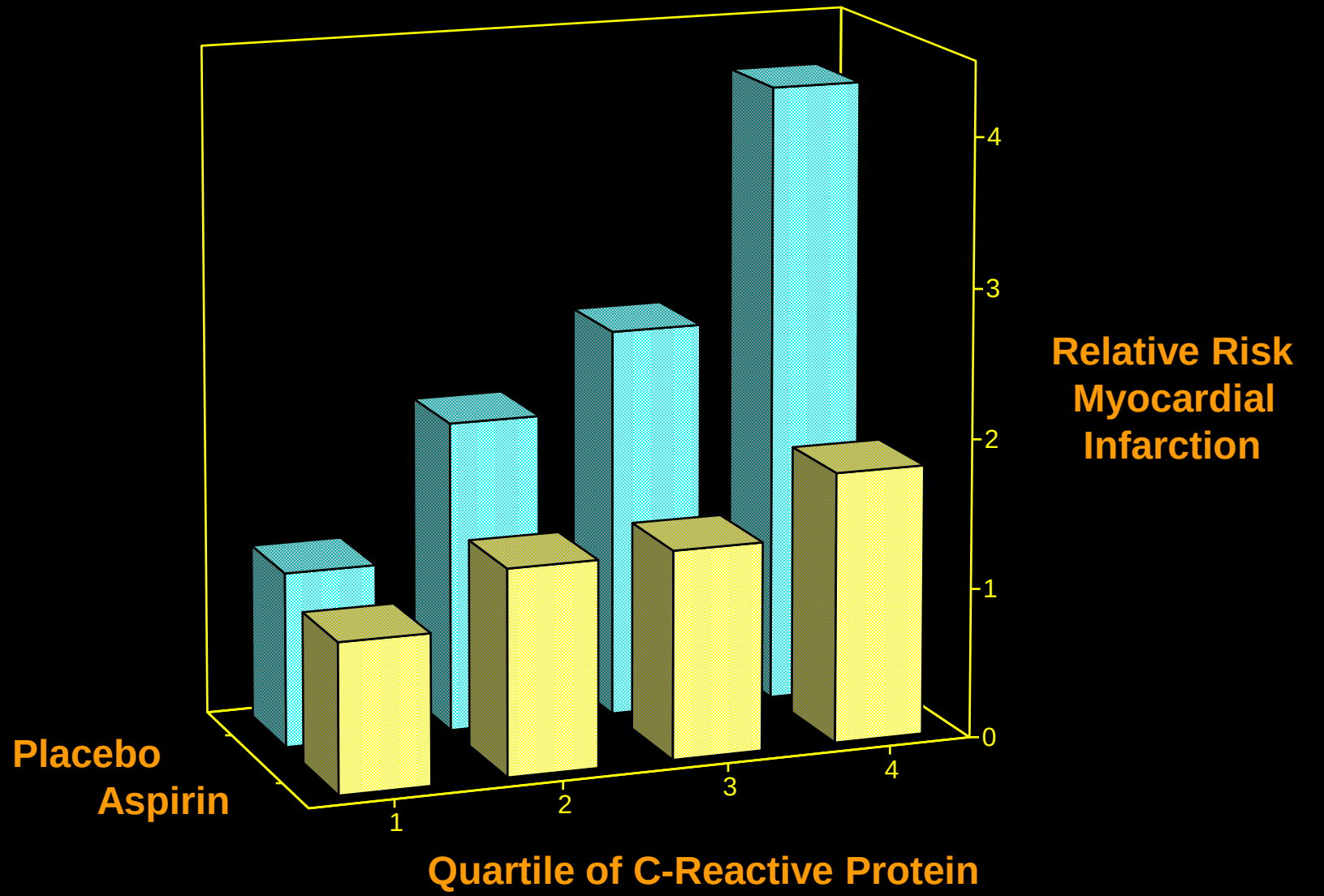
Ridker et al, N Engl J Med **1997;336:973–979.**

hsCRP and Risks of Future MI: Analysis Stratified by Year of Follow-Up



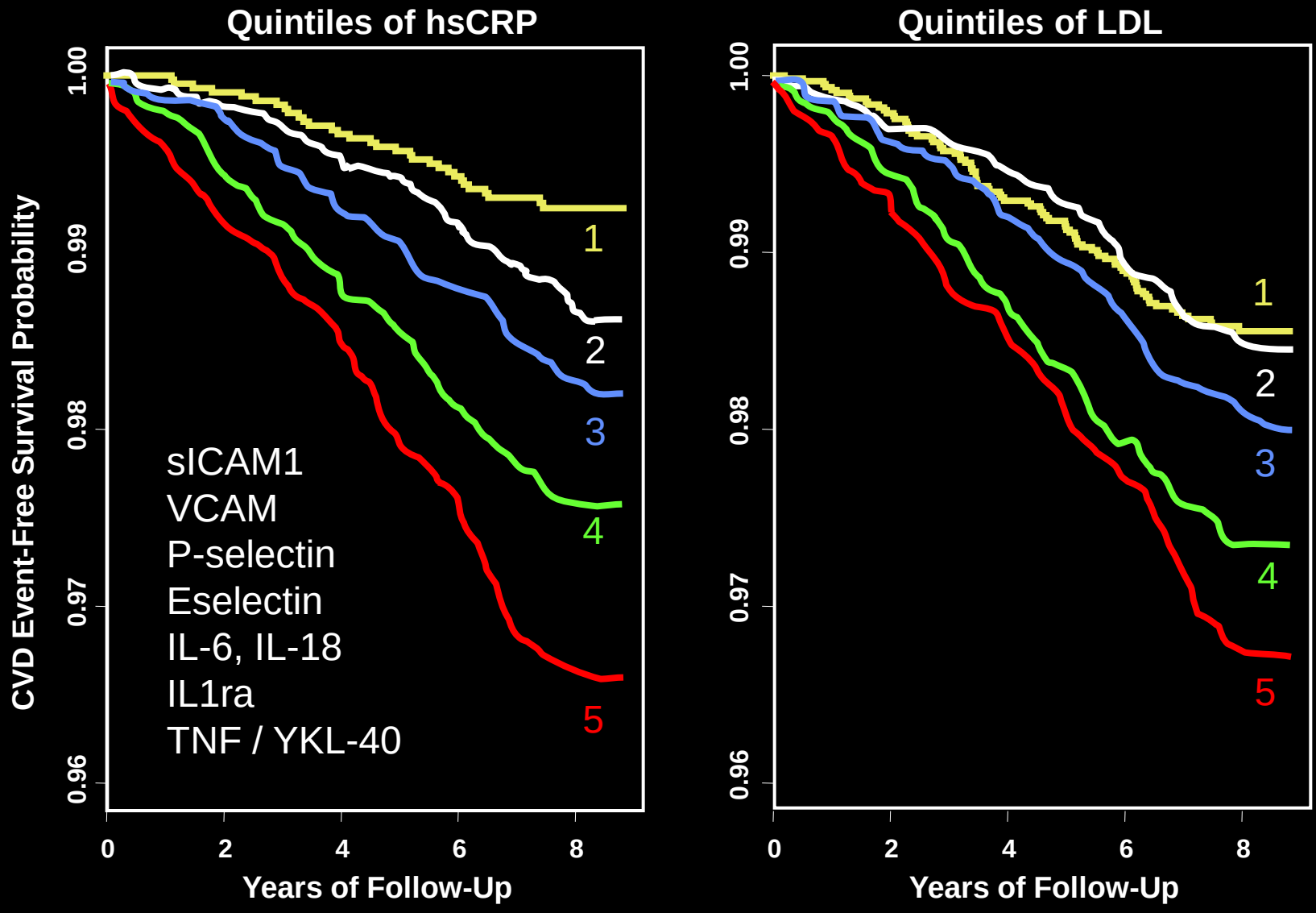
Ridker et al N Engl J Med 1997;336:973-9

hsCRP, Aspirin, and Risks of Future Myocardial Infarction



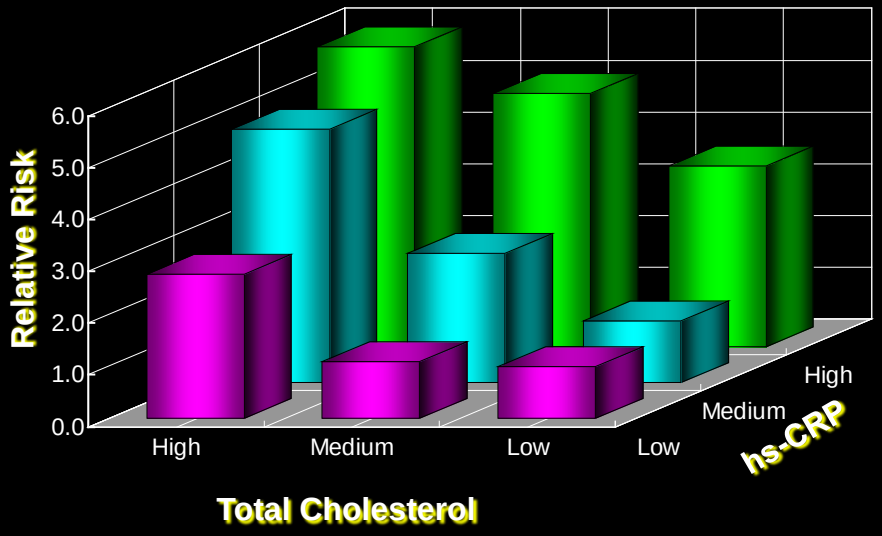
Ridker et al N Engl J Med 1997;336:973-9

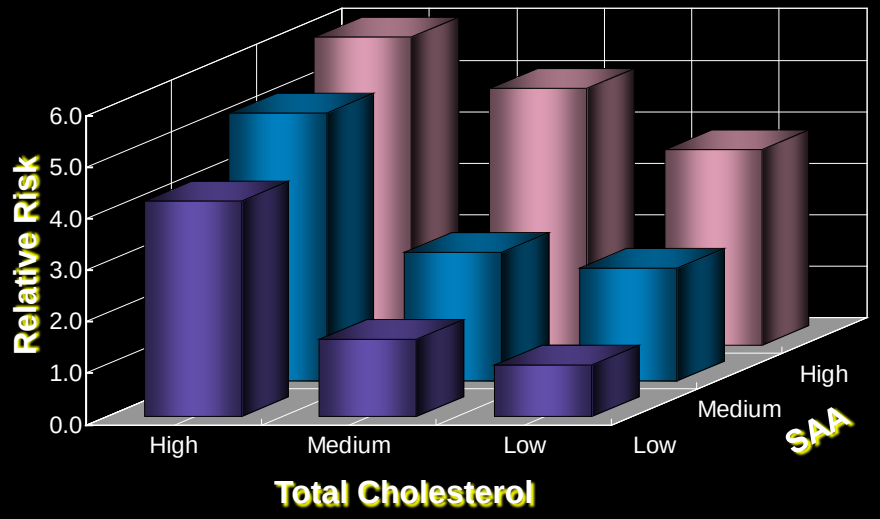
Event-Free Survival According to Baseline Quintiles of hs-CRP and LDL Cholesterol

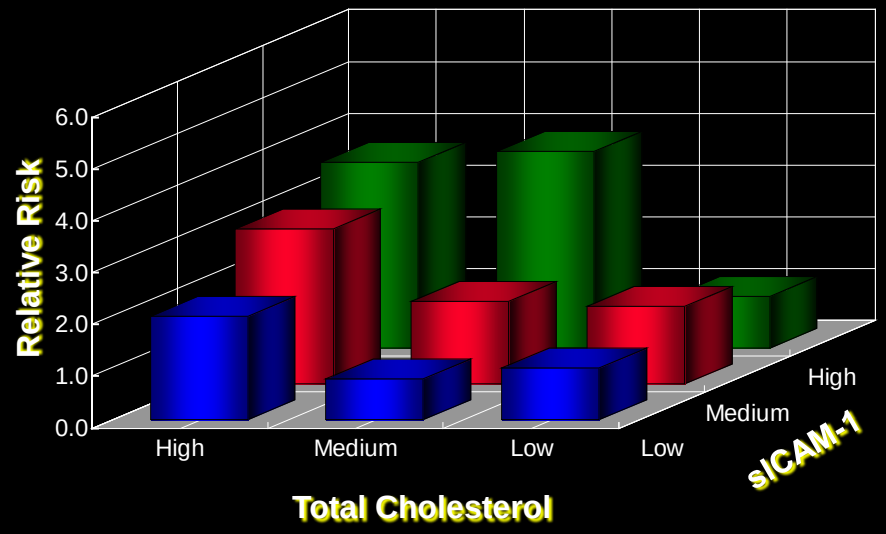


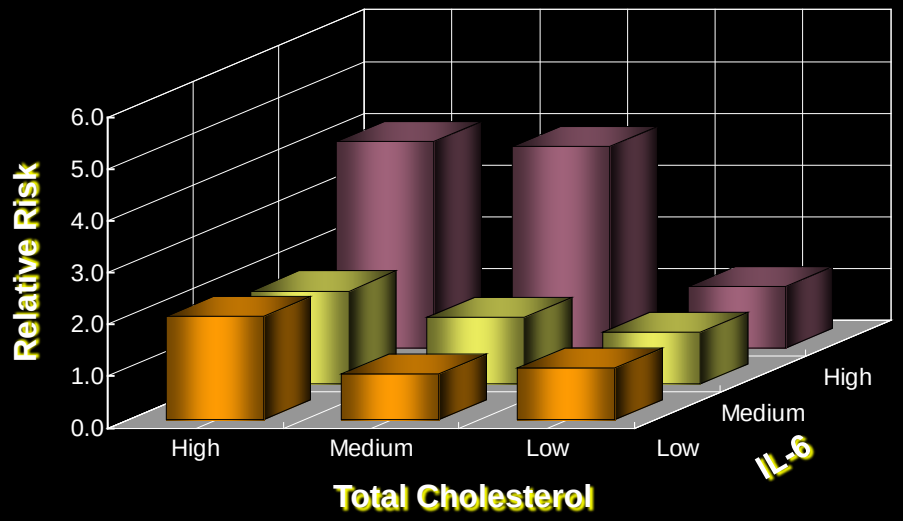
Ridker et al N Engl J Med. 2002;347:1157-1165.

Markers of Inflammation in the Prediction of Cardiovascular Disease in Women









Ridker et al NEJM. 2000;342:836–43.

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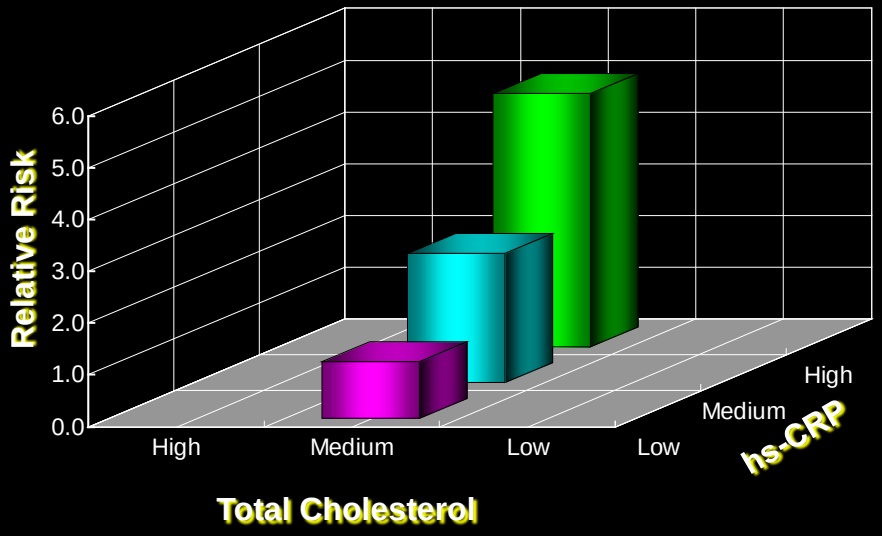

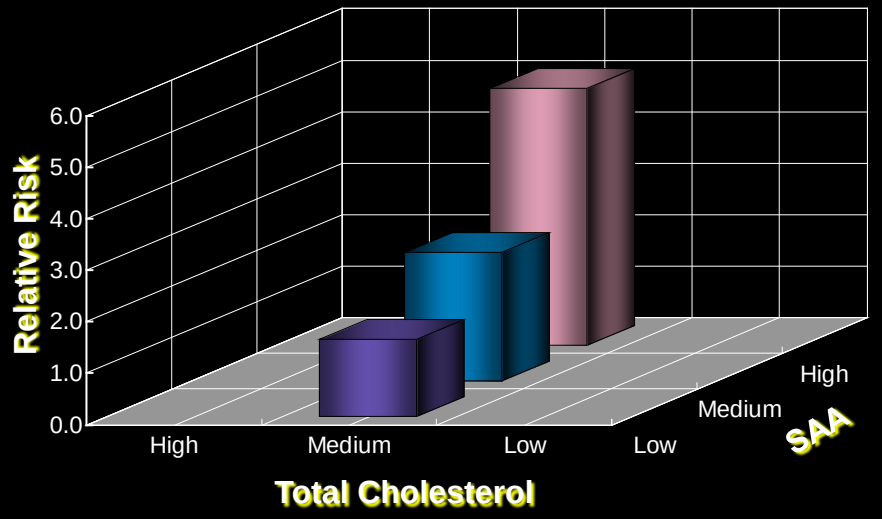

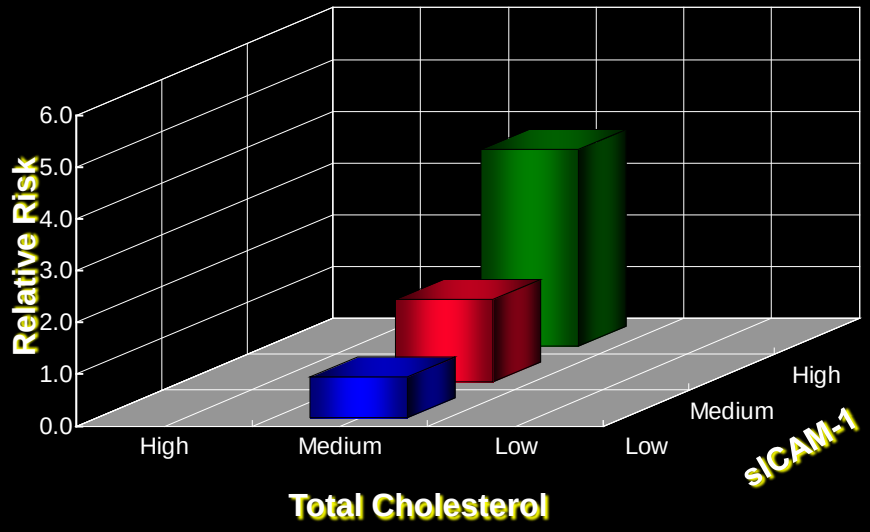

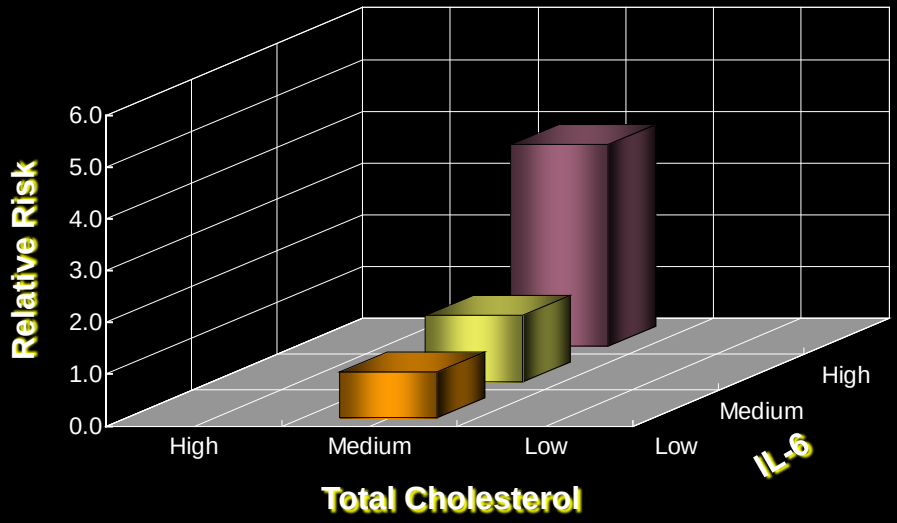

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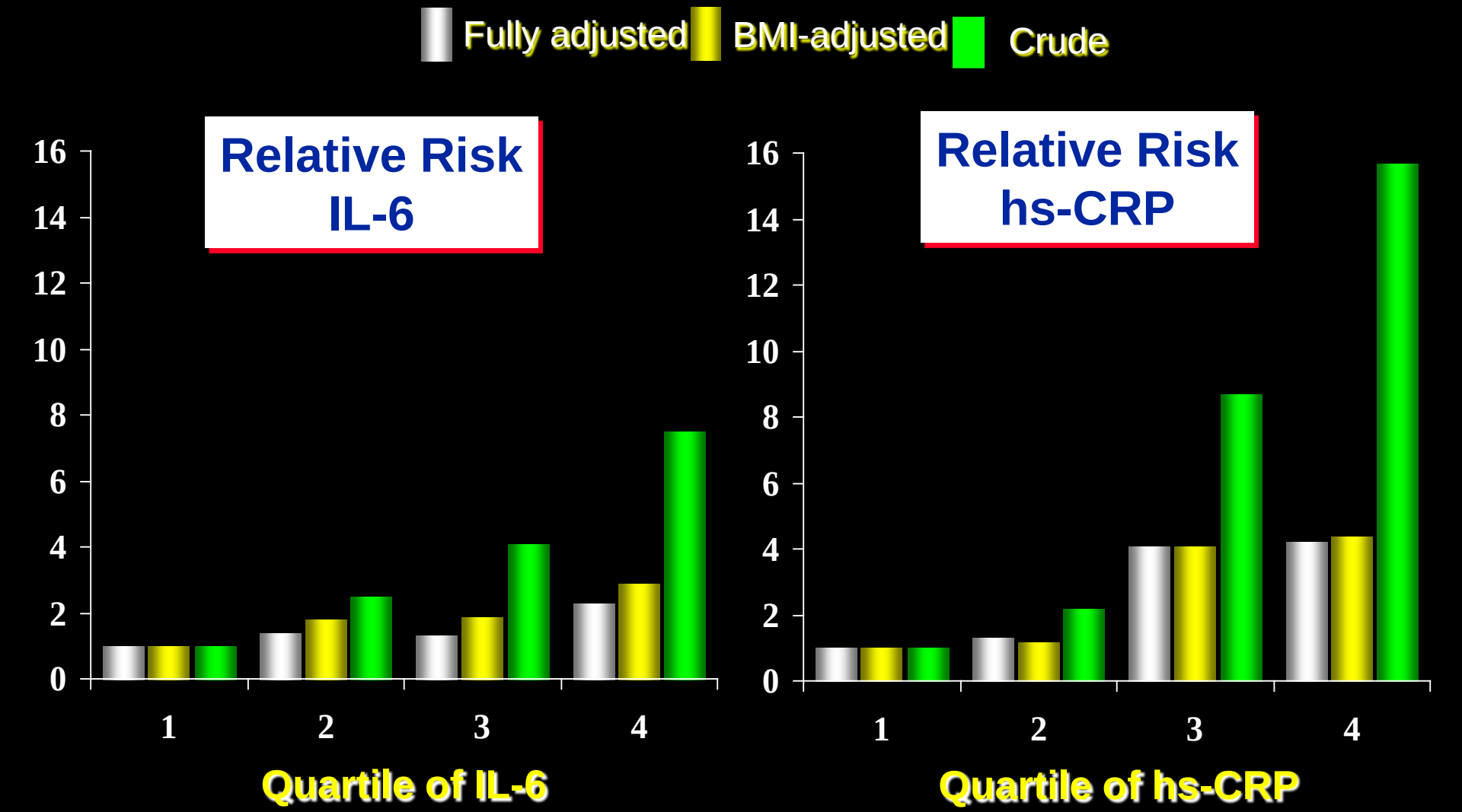
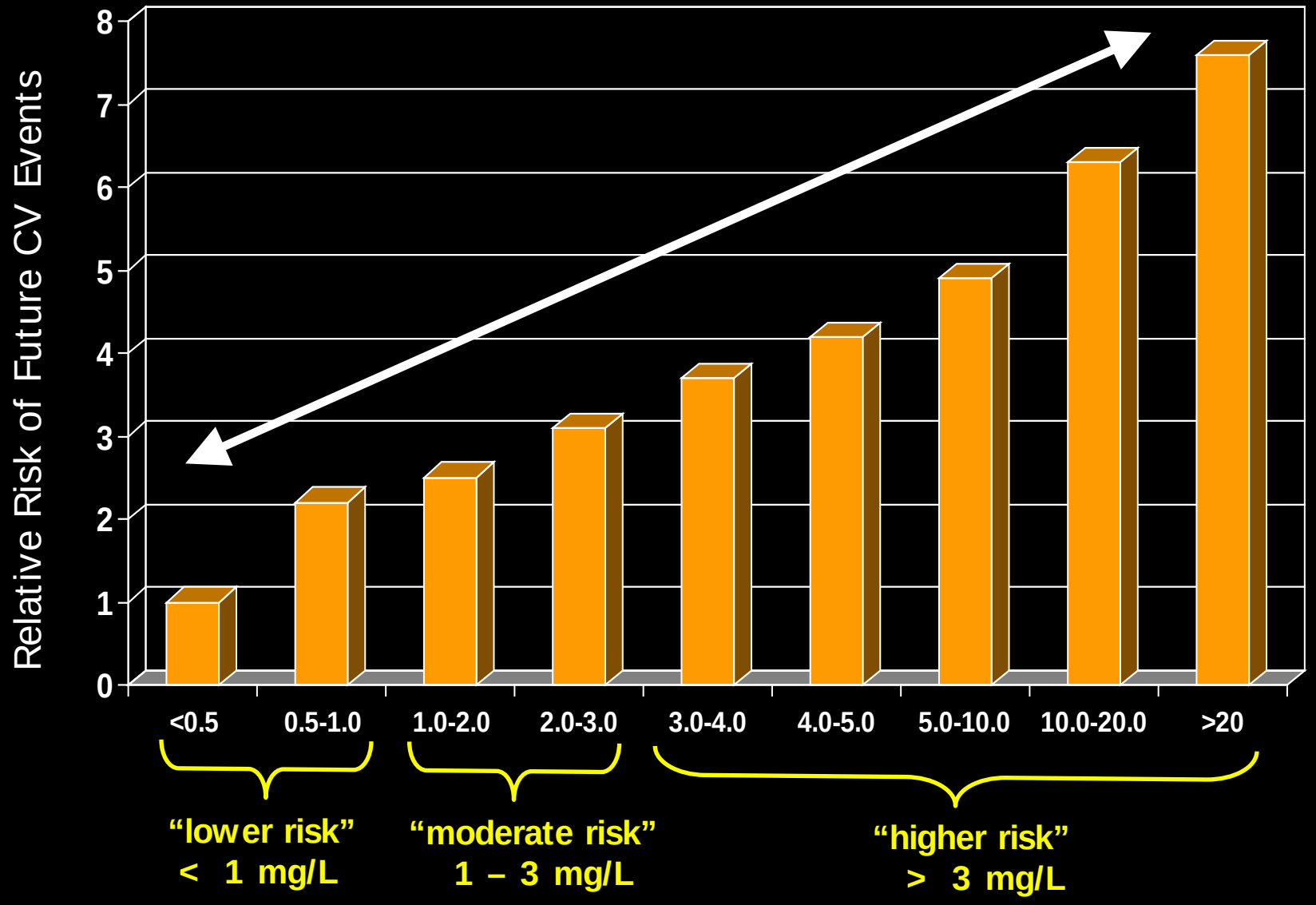
CRP, IL-6 and the Risk for Developing Type-2 Diabetes in the Women's Health Study



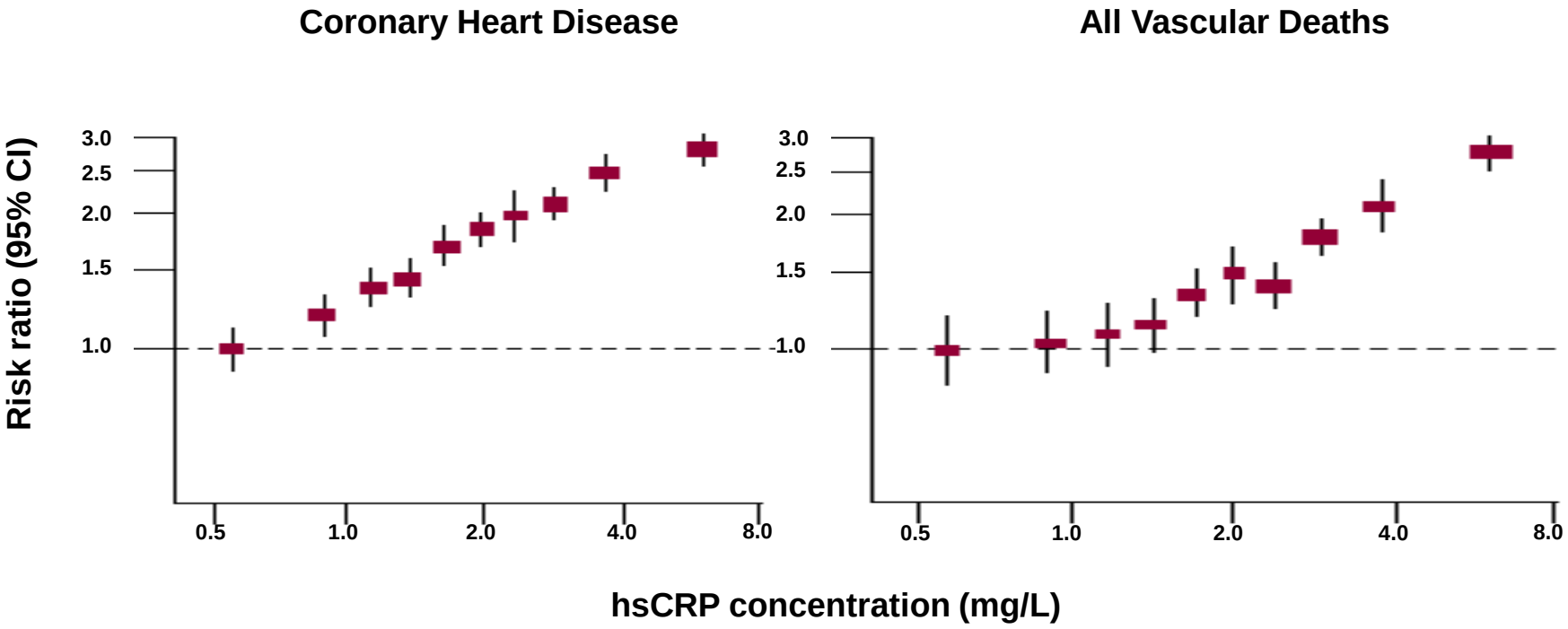
Pradhan et al JAMA 2001; 286:327-34

Linear Relationship of Inflammation to Vascular Risk Across a Very Wide Range of Values



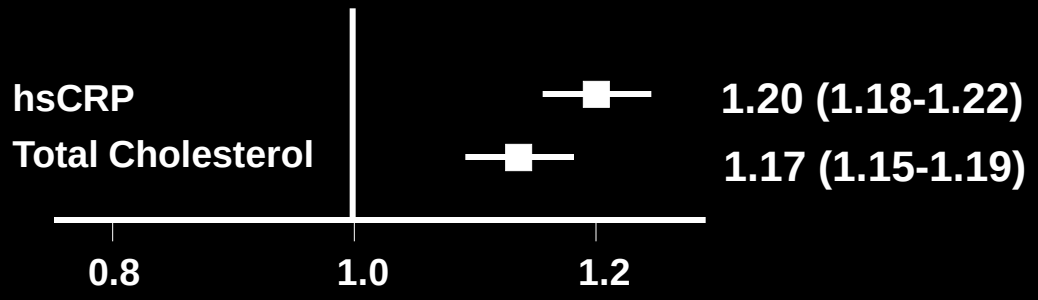
Circulation 2004;109:1955-59

Meta-analysis of 54 Prospective Cohort Studies
hsCRP concentration and risk of cardiovascular events : 2010



Emerging Risk Factor Collaborators, Lancet January 2010

Direct Comparison of Lipid Markers and hsCRP in 166,596 Individuals Followed For First-Onset Cardiovascular Disease (ERFC NEJM 2012;367:1310-1320)



Multivariable Hazard Ratio for CVD per 1-SD change
(adjusted for Age, Gender, Smoking, DM, BP, and HDL)

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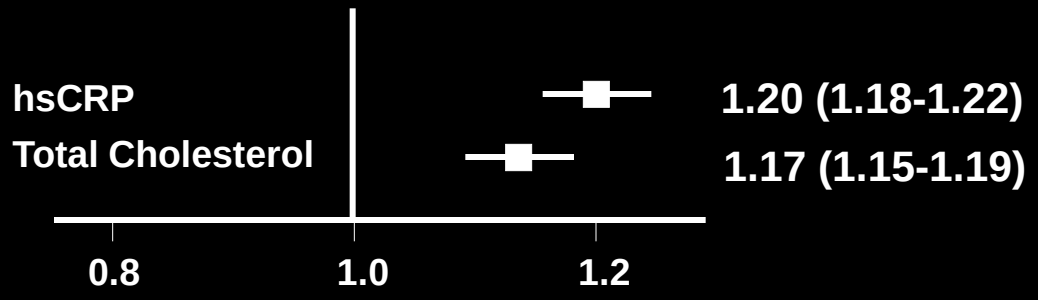

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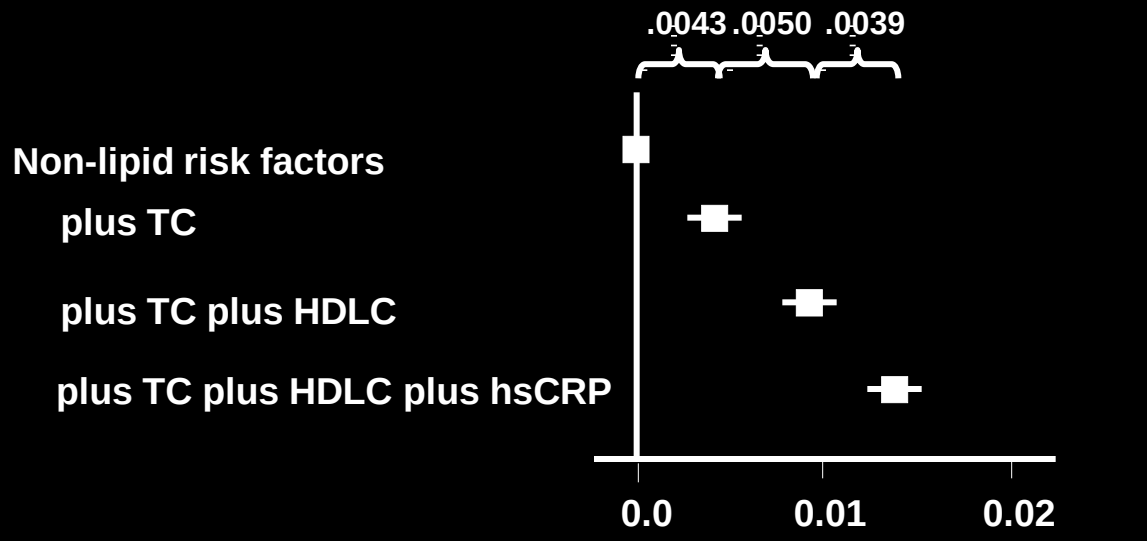


Change in C-statistic
(as compared with non-lipid-based model)

C-Reactive Protein and Reclassification of Cardiovascular Risk in the Framingham Heart Study

Peter W.F. Wilson, MD; Michael Pencina, PhD; Paul Jacques, DS; Jacob Selhub, PhD; Ralph D'Agostino, Sr, PhD; Christopher J. O'Donnell, MD, MPH

Background—The relationship of circulating levels of high-sensitivity C-reactive protein (CRP) with cardiovascular disease (CVD) risk, particularly with consideration of effects at intermediate levels of risk, has not been fully assessed.

Methods and Results—Among 3006 offspring participants in the Framingham Heart Study free of CVD (mean age, 46 years at baseline), there were 129 hard coronary heart disease (CHD) events and 286 total CVD events during 12 years of follow-up. Cox regression, discrimination with area under the receiver operating characteristic curve, and net reclassification improvement were used to assess the role of CRP on vascular risk. In an age-adjusted model that

The net reclassification improvement when CRP was added to traditional risk factors was 11.8 % for hard CHD (P= 0.009), a value greater than that of LDL, HDL, or blood pressure in the Framingham Data

improvement in the discrimination of events. The net reclassification improvement when CRP was added to traditional factors was 5.6% for total CVD (P=0.014) and 11.8% for hard CHD (P=0.009).

Conclusions—Circulating levels of CRP help to estimate risk for initial cardiovascular events and may be used most effectively in persons at intermediate risk for vascular events, offering moderate improvement in reclassification of risk.

(***Circ Cardiovasc Qual Outcomes*. 2008;1:92-97.)**

Key Words: epidemiology ■ inflammation ■ risk factors ■ statistics

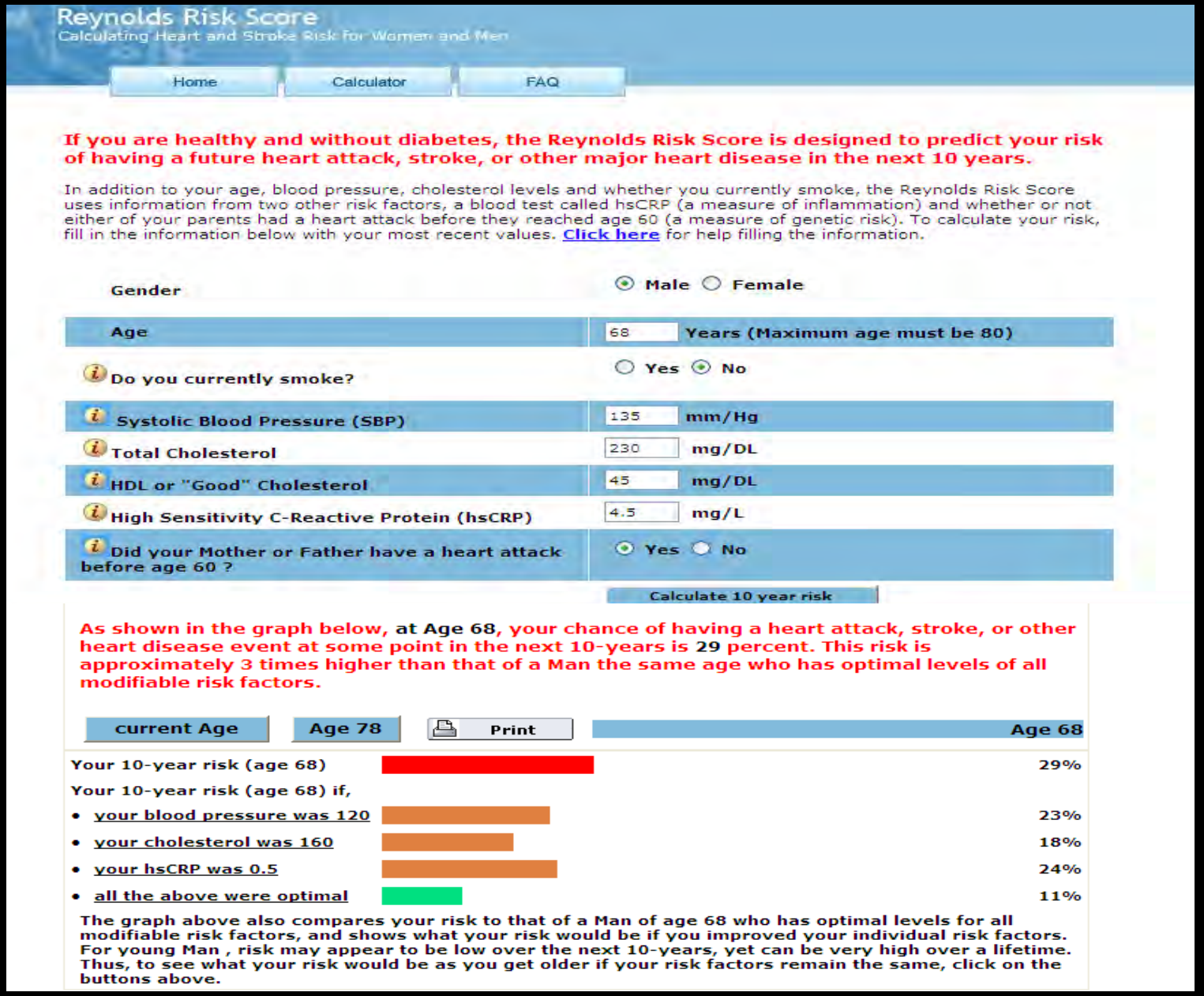
Wilson P, et al Circ Cardiovasc Qual Outcomes 2008;1:92-97

www.reynoldsriskscore.org

Reynolds Risk Score

Age
Smoking
SBP
TC
HDLC
hsCRP
Family History
HbA1c

hsCRP (mg/L) is not CRP (mg/dL)



Comparison of the Framingham and Reynolds Risk Scores for Global Cardiovascular Risk Prediction in the Multiethnic Women's Health Initiative

Nancy R. Cook, ScD; Nina P. Paynter, PhD; Charles B. Eaton, MD; JoAnn E. Manson, MD, DrPH; Lisa W. Martin, MD; Jennifer G. Robinson, MD, MPH; Jacques E. Rossouw, MD; Sylvia Wassertheil-Smoller, PhD; Paul M Ridker, MD

Background—Framingham-based and Reynolds Risk scores for cardiovascular disease (CVD) prediction have not been directly compared in an independent validation cohort.

Methods and Results—We selected a case-cohort sample of the multiethnic Women's Health Initiative Observational Cohort, comprising 1722 cases of major CVD (752 myocardial infarctions, 754 ischemic strokes, and 216 other CVD deaths) and a random subcohort of 1994 women without prior CVD. We estimated risk using the Adult Treatment Panel

"The Reynolds Risk Score was better calibrated than the Framingham model in this large external validation cohort. The Reynolds score also showed improved discrimination overall in black and white women. Large differences in risk estimates exist between models, with clinical implications for statin therapy."

$P=0.02$), and positive integrated discrimination improvement (4.1%; $P<0.0001$) overall, excluding diabetics (NRI=4.2%; $P=0.01$), and in white (NRI=4.3%; $P=0.04$) and black (NRI=11.4%; $P=0.13$) women. The Reynolds (NRI=12.9%; $P<0.0001$) and ATP-III (NRI=5.9%; $P=0.0001$) models demonstrated better discrimination than the Framingham CVD model.

Conclusions—The Reynolds Risk Score was better calibrated than the Framingham-based models in this large external validation cohort. The Reynolds score also showed improved discrimination overall and in black and white women. Large differences in risk estimates exist between models, with clinical implications for statin therapy. **(*Circulation*. 2012;125:1748-1756.)**

Cook NR et al, Circulation 2012;125:1748-1756

55 year old executive
Chief complaint
Stress and anxiety
No prior CV history
Non-smoker, no diabetes
Close associate recurrent MI
“elevated CRP”

TC 170

HDL 42

LDL 112

TG 80

hs-CRP 0.6

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55 year old executive
Chief complaint
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TC 170

HDL 42

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TG 80

hs-CRP 0.6

Checkup Finds Bush Fit and Healthy

By LAWRENCE K. ALTMAN

WASHINGTON, Aug. 4 — President Bush is in "outstanding health" and at very low risk for a heart attack, his doctors said today after performing Mr. Bush's first medical checkup since he took office.

Mr. Bush was monitored while he ran on a treadmill for 26 minutes with a maximum heart rate of 178 beats per minute. The findings placed him "in the top 2 percent of men his age in cardiovascular fitness," a White House statement signed by 14 doctors said.

Mr. Bush, 55, runs an average of three miles four times a week. He also swims, lifts weights and uses an elliptical trainer. His resting heart rate was reported as 43 beats a minute and his blood pressure as 118/74.

Mr. Bush, who is six feet tall, has lost nearly five pounds in the last year. His weight of 189.75 pounds is down from 194.5 pounds at his last checkup in June 2000, when he was governor of Texas. His body fat is normal at 14.5 percent, down from 19.94 percent.

"I'm in pretty good shape," Mr. Bush said after after completing the 5-hour, 50-minute examination at Bethesda Naval Hospital.

The only new abnormality reported was the removal of three potentially cancerous lesions from Mr. Bush's face. Dr. Richard A. Keller, the chief dermatologist at Walter Reed Army Medical Center, used liquid nitrogen to remove the lesions, which are known as actinic keratoses. They are common and result from chronic sun exposure; if untreated, a small percentage of them can become skin cancers. A White House spokesman described them as "small, dry patches" that had a red tint and felt "like sandpaper."

In 1998 and 1999, Mr. Bush had benign polyps removed from his colon after a routine examination. Another colonoscopy is not due until next year, the doctors said. Ultrasound tests of his abdomen performed today were normal.

Tests showed no change in Mr. Bush's mild high-frequency hearing loss, which does not affect his normal conversations.

A set of 70 blood and urine tests were all normal. They included tests for risk of heart disease: total cholesterol, 170; high density lipoprotein, 42; low density lipoprotein, 112; trigylcerides 80; C-reactive protein, 0.4; and homocysteine, 8.6. A standard blood test for prostate cancer was a normal 0.78.

Mr. Bush suffers from seasonal allergies, wears reading glasses, smokes an occasional cigar and does not drink alcohol, according to the statement.

He takes vitamins but does not routinely use prescription medications and has not missed a day of work since his last checkup. The examination was performed by Dr. Kenneth H. Cooper of Dallas, who has given Mr. Bush annual checkups since 1989.

Dr. Cooper joined Dr. Richard J. Tubb, the White House physician, in supervising today's checkup.

The 14 doctors used a standard military phrase to describe Mr. Bush as "fit for duty." All but four of the doctors work at military hospitals. They also said, "All data suggest that he will remain so for the duration of his presidency."

NYT
August 4
2001

Doctors Who Examine Bush Say He Is Exceptionally Fit

By LAWRENCE K. ALTMAN

WASHINGTON, Aug. 6 — President Bush's second annual medical checkup since he took office found him in "extraordinary health," his doctors said today, with his heart and lung function in the top 1 percent for men of his age, up from the top 2 percent a year ago.

The three-hour battery of tests that Mr. Bush, 56, underwent this morning show that he has no evidence of heart disease and a "very low" risk for a heart attack, the doctors said. They predicted that he would remain in excellent health for the rest of his term.

As Mr. Bush returned to the White House from the National Naval Medical Center in nearby Bethesda, Md., where the checkup was performed, he said he was "feeling good." Later, Mr. Bush flew to his ranch in Texas for a monthlong working vacation.

In a five-page detailed statement released by the White House, the team of eight military and civilian doctors and health specialists who examined the president said that Mr. Bush had not missed work due to illness in the White House and that he had not had a recurrence of the fainting episode he suffered in January when a pretzel stuck in his throat.

Mr. Bush fell off a sofa and cut his face in the fainting incident, which the White House said occurred while he was watching television.

Mr. Bush smokes an occasional cigar, abstains from alcohol and drinks diet sodas and coffee, the doctors said. Mr. Bush, who stands six feet tall, weighed 189 pounds, three-quarters of a pound less than at the checkup in August 2001. His body fat remained unchanged at 14.5 percent and down from 19.94 percent recorded in a checkup in June 2000.

He takes vitamins and an aspirin daily. Mr. Bush does not routinely use prescription medications except for a steroid nasal spray to prevent symptoms in allergy seasons.

The only abnormalities noted involved his hearing, skin and eyes.

Mr. Bush has a high frequency hearing loss in both ears from 4,000 to 8,000 kilohertz that is unchanged from last year's examination. Mr. Bush's hearing is excellent in the frequencies for speech, the doctors said. They also said that the degree and frequency involved do not affect normal conversation.

The doctors said that the small harmless red blotches that appear on Mr. Bush's nose are due to widened capillaries resulting from sun exposure. No treatment was given today, but they said that it may be needed in the future for the condition, known as telangiectasias. It is common.

In the last year, four small benign skin growths were removed from Mr. Bush's face.

Mr. Bush occasionally uses reading glasses.

Mr. Bush is a fitness enthusiast, and his heart rate of 44 beats a minute and blood pressure of 106/70 reflected his training routine. He typically runs three miles four times a week, with average times from 6:45 minutes to 7:15 minutes a mile. He also routinely cross-trains with free weights for 45 minutes twice a week and an eliptical trainer.

In an exercise treadmill test during the checkup, Mr. Bush ran for 27:03 minutes with a maximum heart rate of 169, or 97 percent of predicted heart rate, compared to 26 minutes last year.

An echocardiogram, or ultrasound test of the heart, was normal.

Blood tests showed that Mr. Bush's total cholesterol was in the "desirable" level, at 177. His high density lipoprotein (HDL) was normal at 49. His low density lipoprotein (LDL) was in the "desirable/near optimal" level of 114, and the ratio of the total cholesterol to HDL was optimal at 3.6, the doctors said.

Additional tests for potential heart disease were also normal. They included triglycerides (69) and homocysteine (7.1). A test for C-reactive protein was 0.6, putting him in the

An annual physical shows the president to be in better shape than last year.

Additional tests for potential heart disease were also normal. They included triglycerides (69) and homocysteine (7.1). A test for C-reactive protein was 0.6, putting him in the lowest risk category.

NYT August 6, 2002

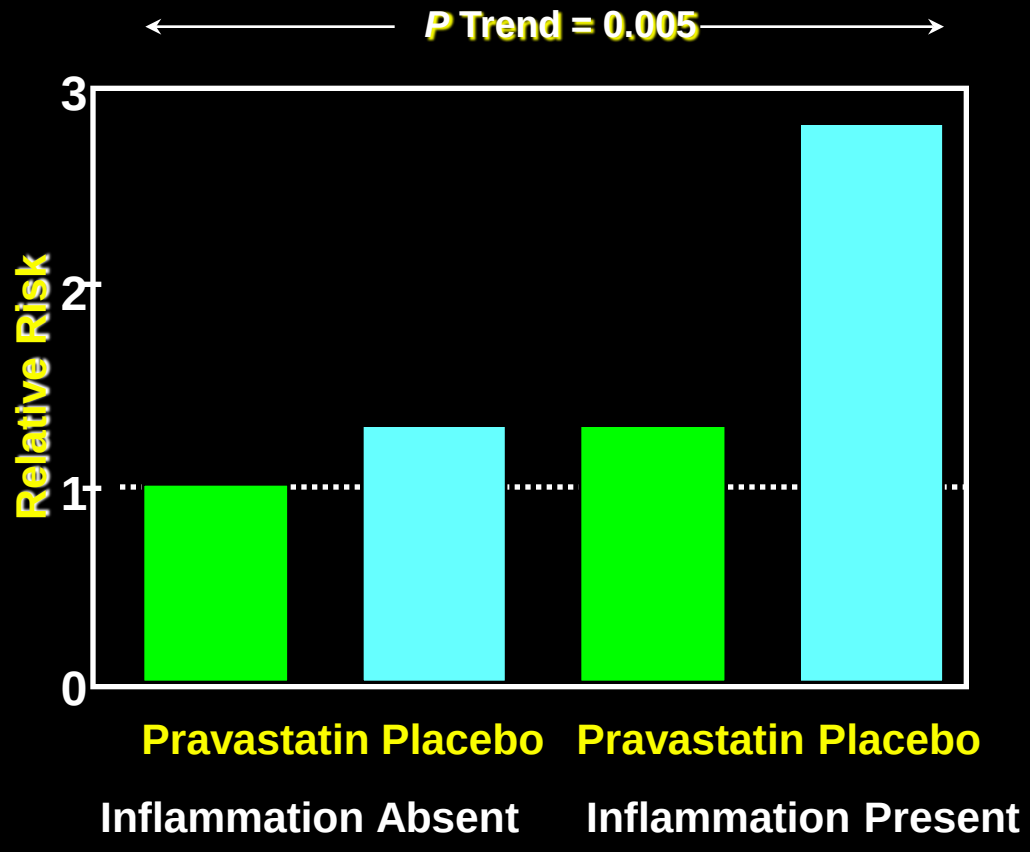
Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions

Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? 1995-2002

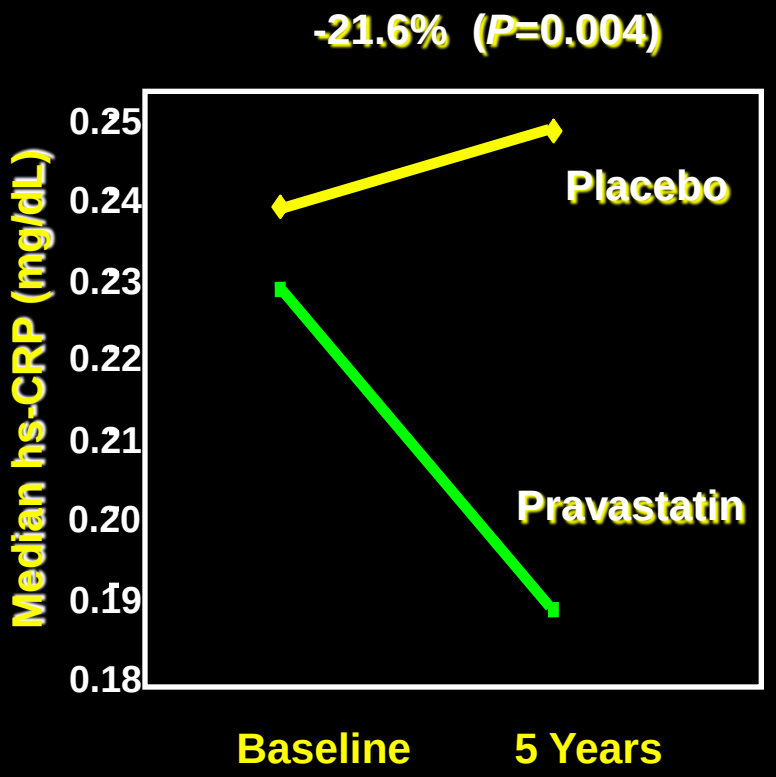
Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? 2002-2008

Is there evidence that reducing inflammation per se will reduce vascular events? 2009 -

Inflammation, Statin Therapy, and hsCRP: Initial Observations

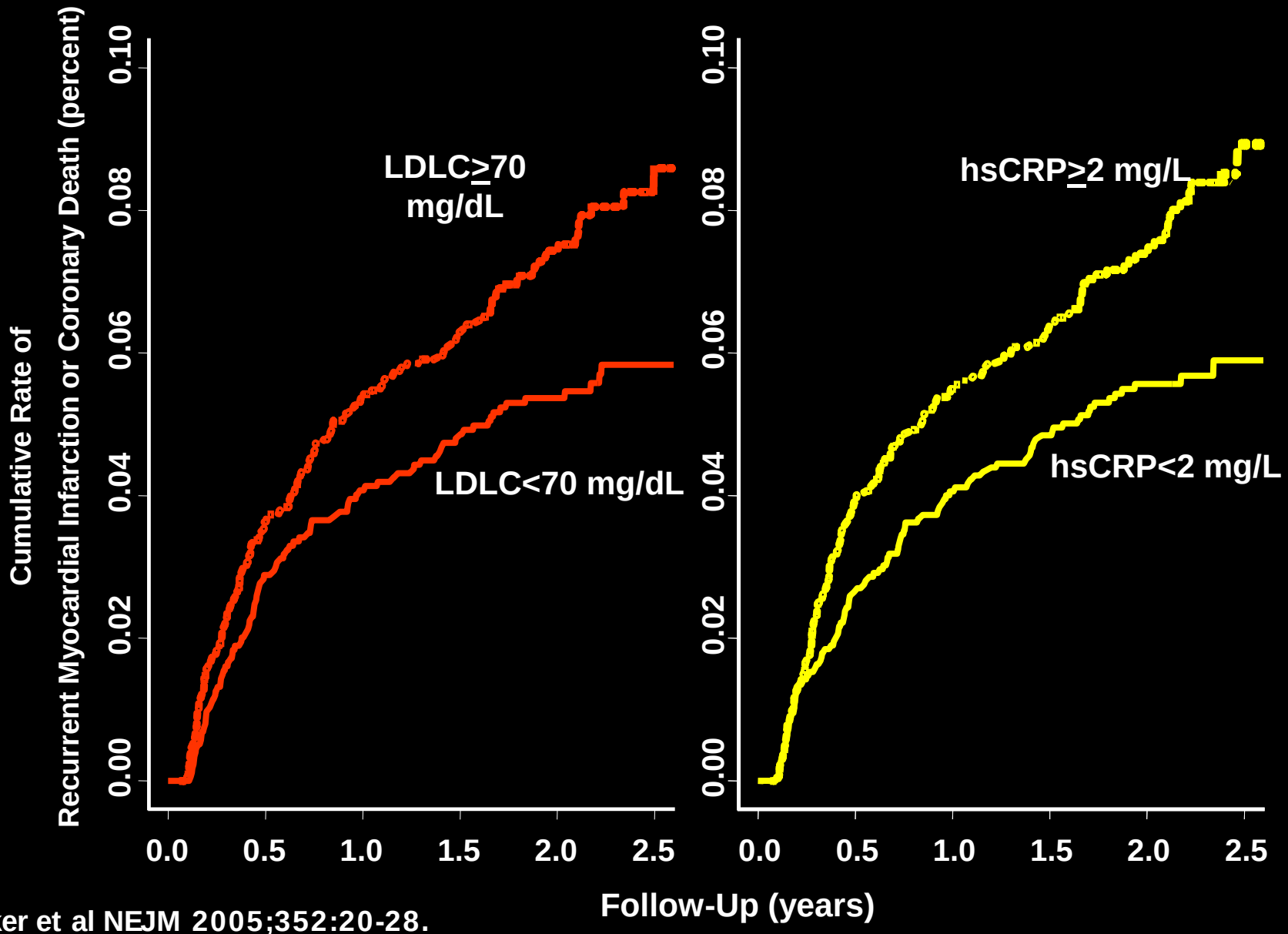


Ridker et al Circulation. 1998;98:839–844.



Ridker et al Circulation. 1999;100:230-235.

Clinical Relevance of Achieved LDL and Achieved CRP After ACS Treated with Statin Therapy



Ridker et al NEJM 2005;352:20-28.

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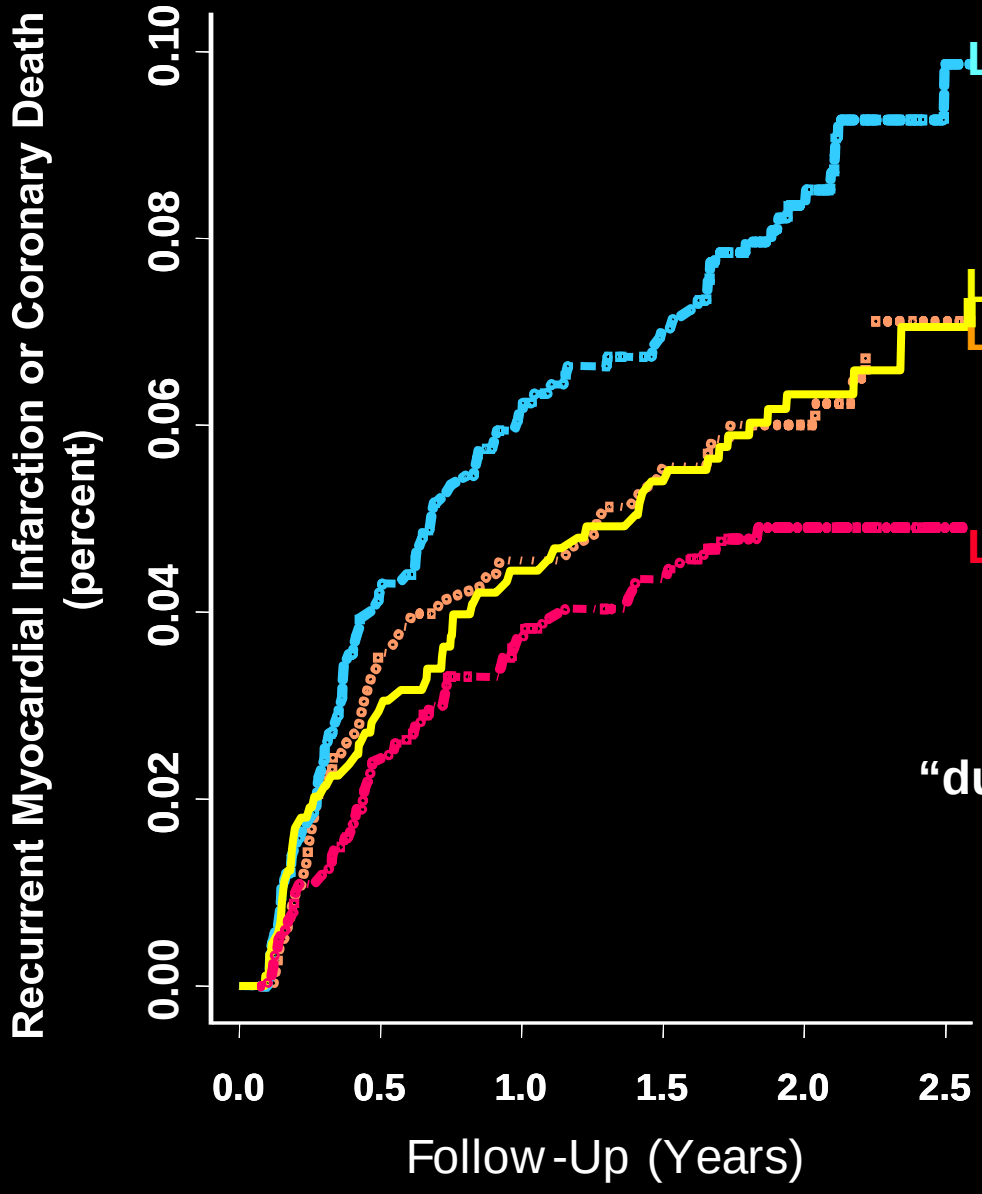
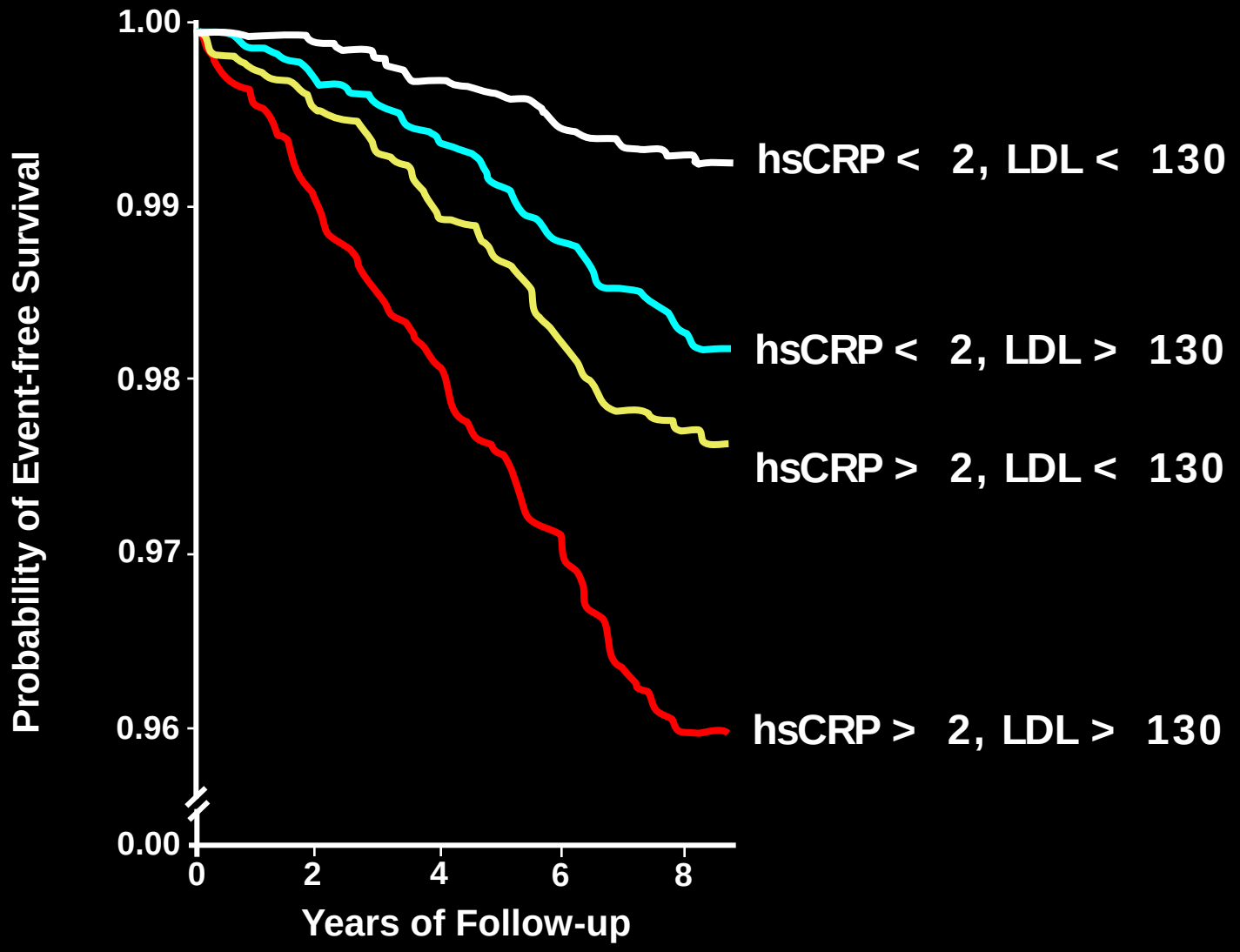


"dual targets for statin therapy"

Ridker et al NEJM 2005;352:20-28.

Primary Prevention : Whom Should We Treat ?



N Engl J Med. 2002;347:1157-1165.

hsCRP as a Method to Target Statin Therapy in Primary Prevention: AFCAPS/TexCAPS

Study Group	Statin	Placebo	NNT
low LDLC / low CRP	0.025	0.022	----
low LDLC / high CRP	0.029	0.051	48
high LDLC / low CRP	0.020	0.050	33
high LDLC / high CRP	0.038	0.055	58

Median LDLC = 150 mg/dL
Median CRP = 2 mg/L

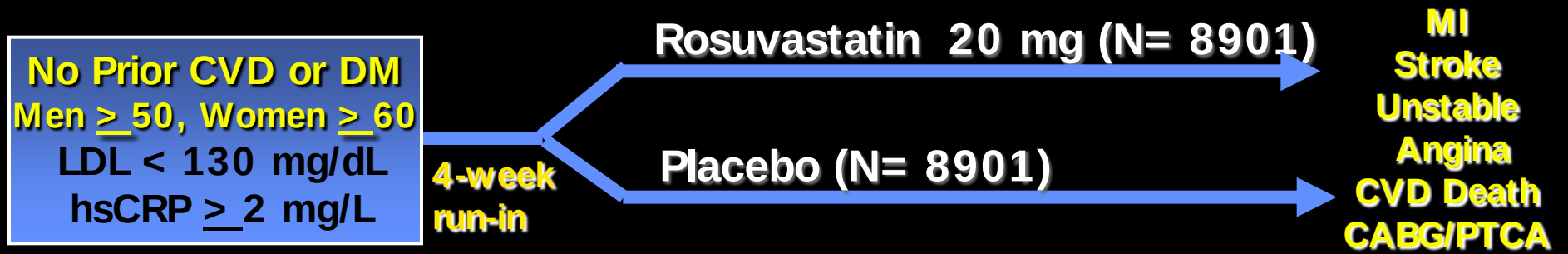
Ridker et al N Engl J Med 2001;344:1959-65

JUPITER Trial Design

Ridker et al NEJM 2008;359:2195-2207

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



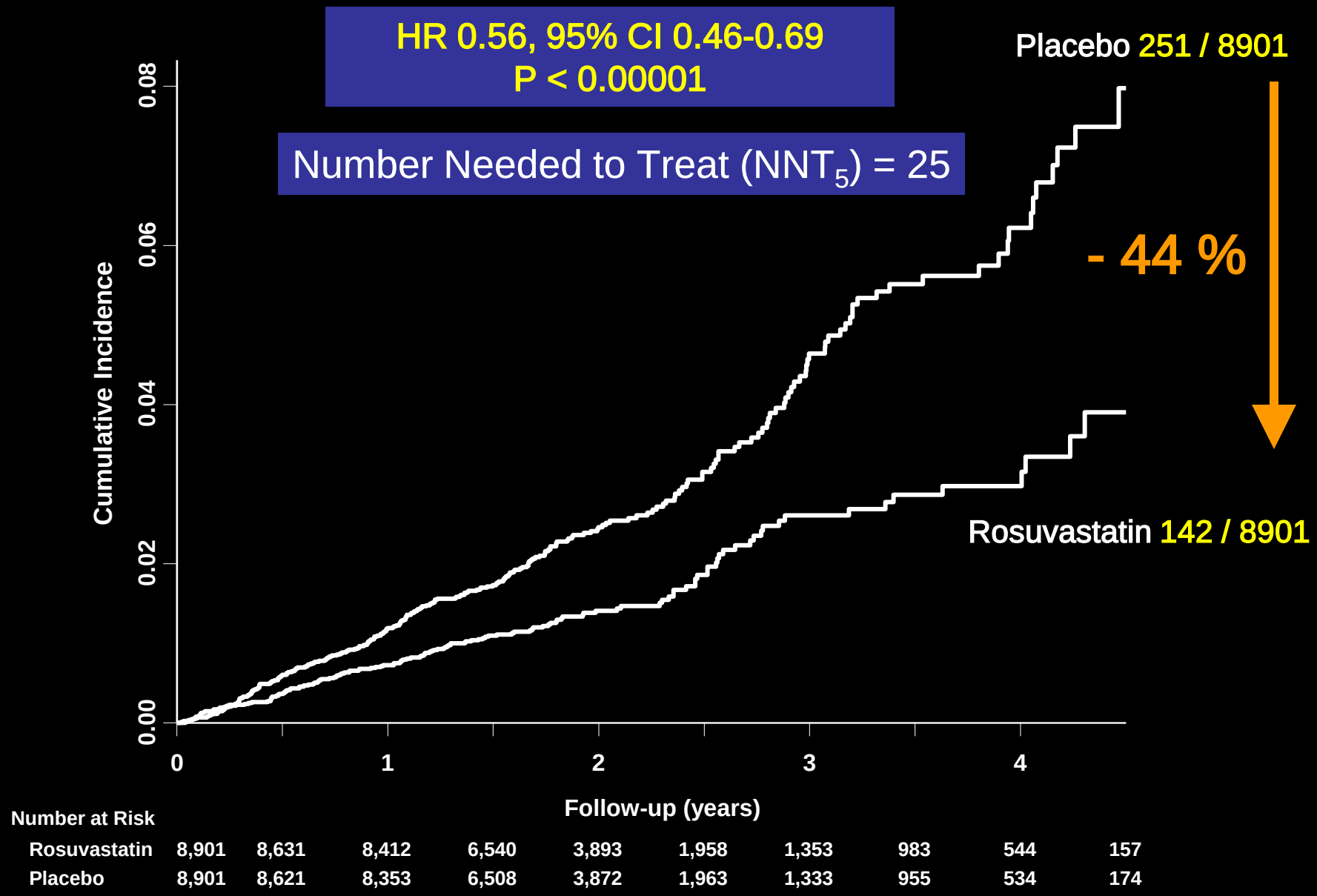
Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Mean LDLC 104 mg/dL, Mean HDLC 50 mg/dL, hsCRP 4 mg/L

JUPITER

Ridker et al NEJM 2008;359:2195-2207

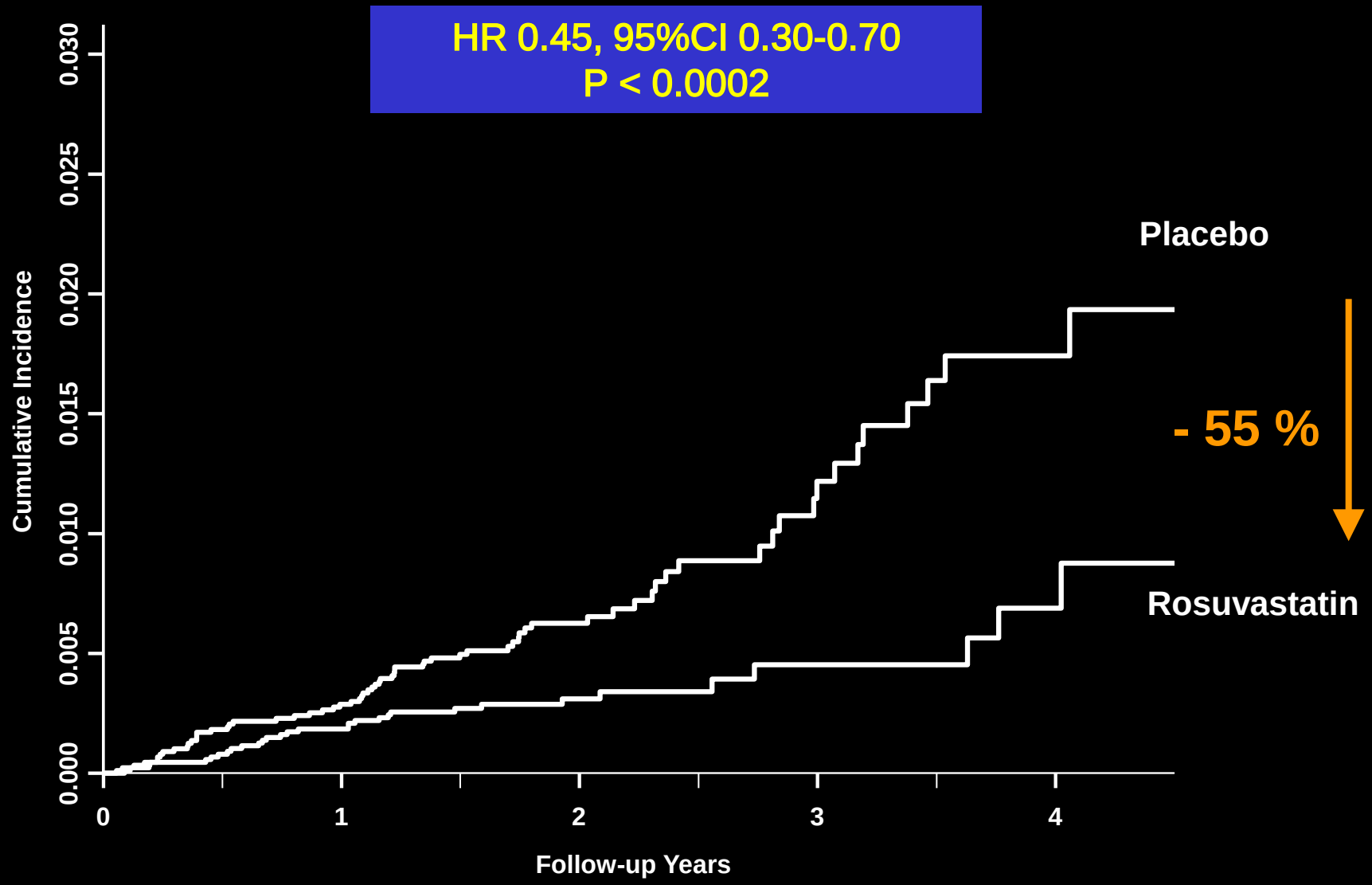
Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



JUPITER

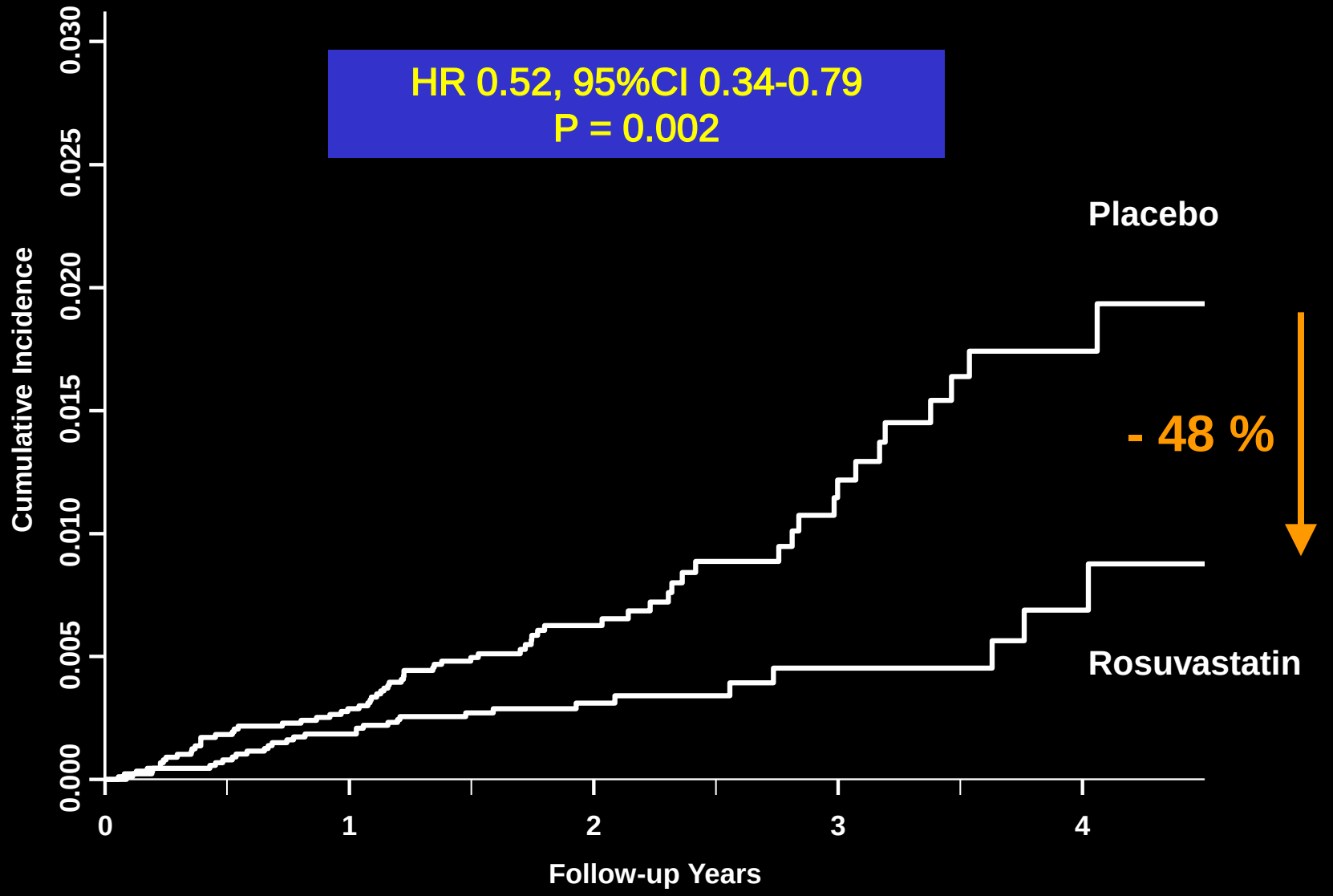
Ridker et al NEJM 2008;359:2195-2207

Fatal or Nonfatal Myocardial Infarction



JUPITER
Fatal or Nonfatal Stroke

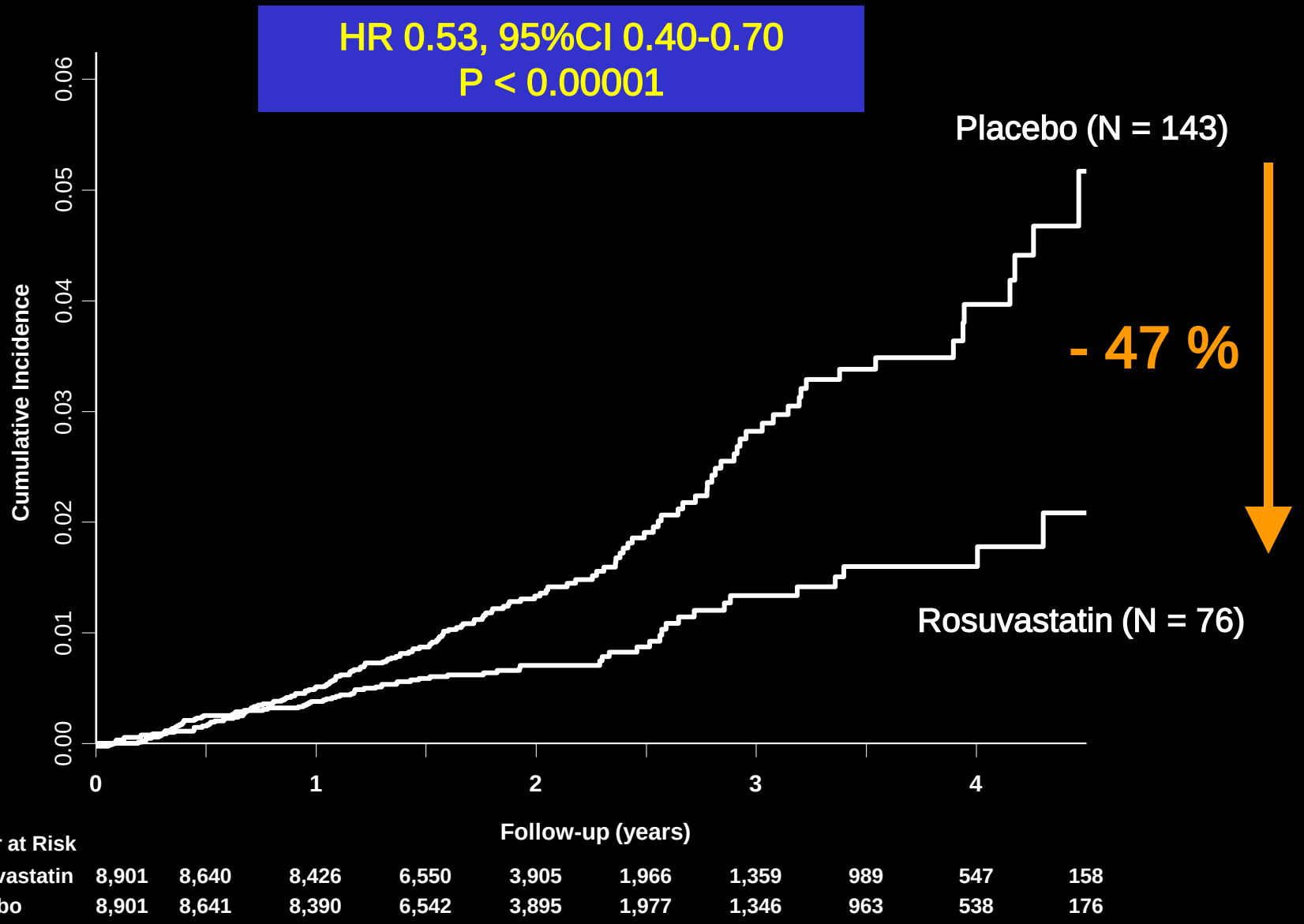
Ridker et al NEJM 2008;359:2195-2207



JUPITER

Ridker et al NEJM 2008;359:2195-2207

Arterial Revascularization / Unstable Angina



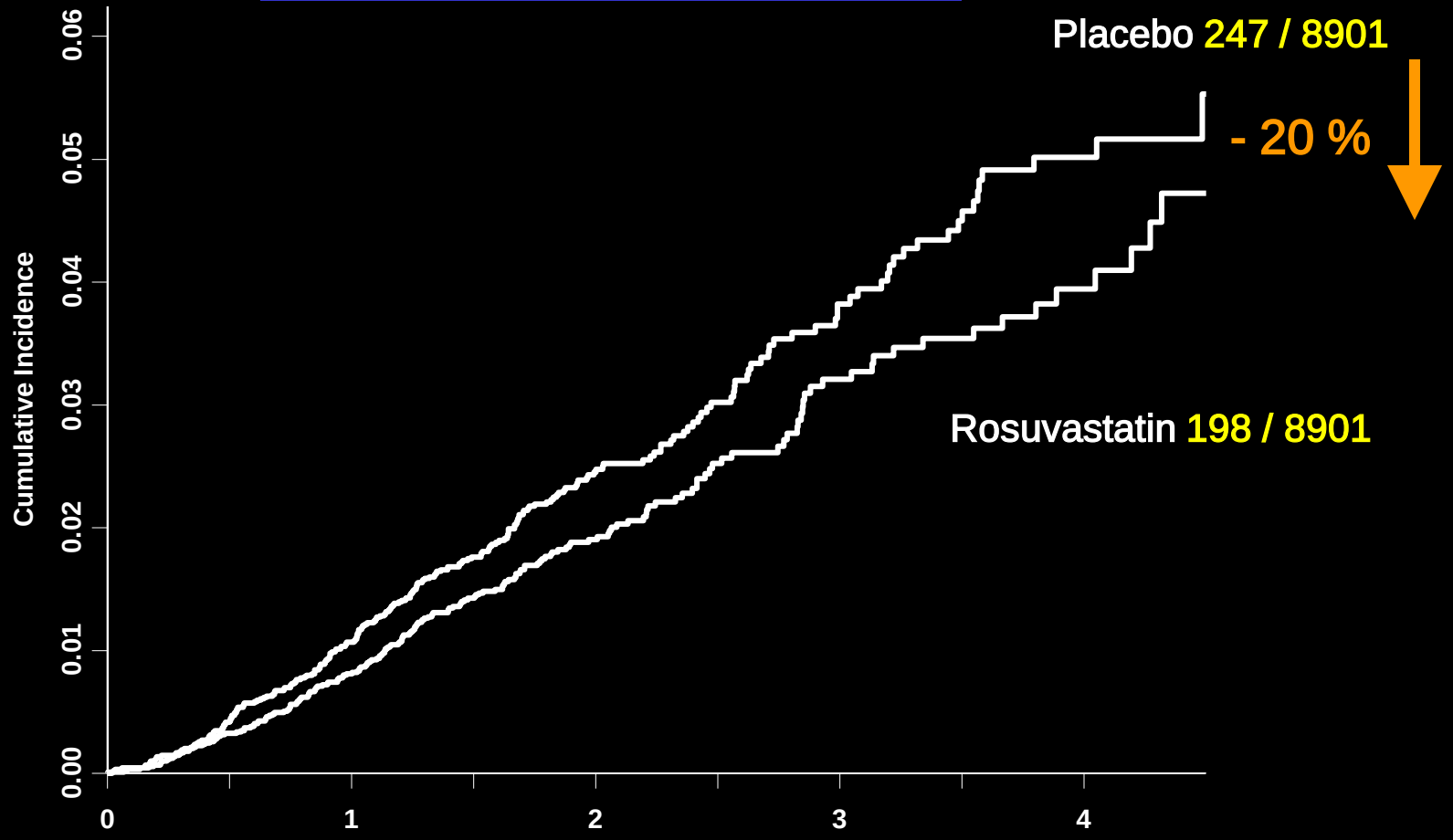
Number at Risk										
Rosuvastatin	8,901	8,640	8,426	6,550	3,905	1,966	1,359	989	547	158
Placebo	8,901	8,641	8,390	6,542	3,895	1,977	1,346	963	538	176

JUPITER

NEJM 2008;359:2195-2207

Secondary Endpoint – All Cause Mortality

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

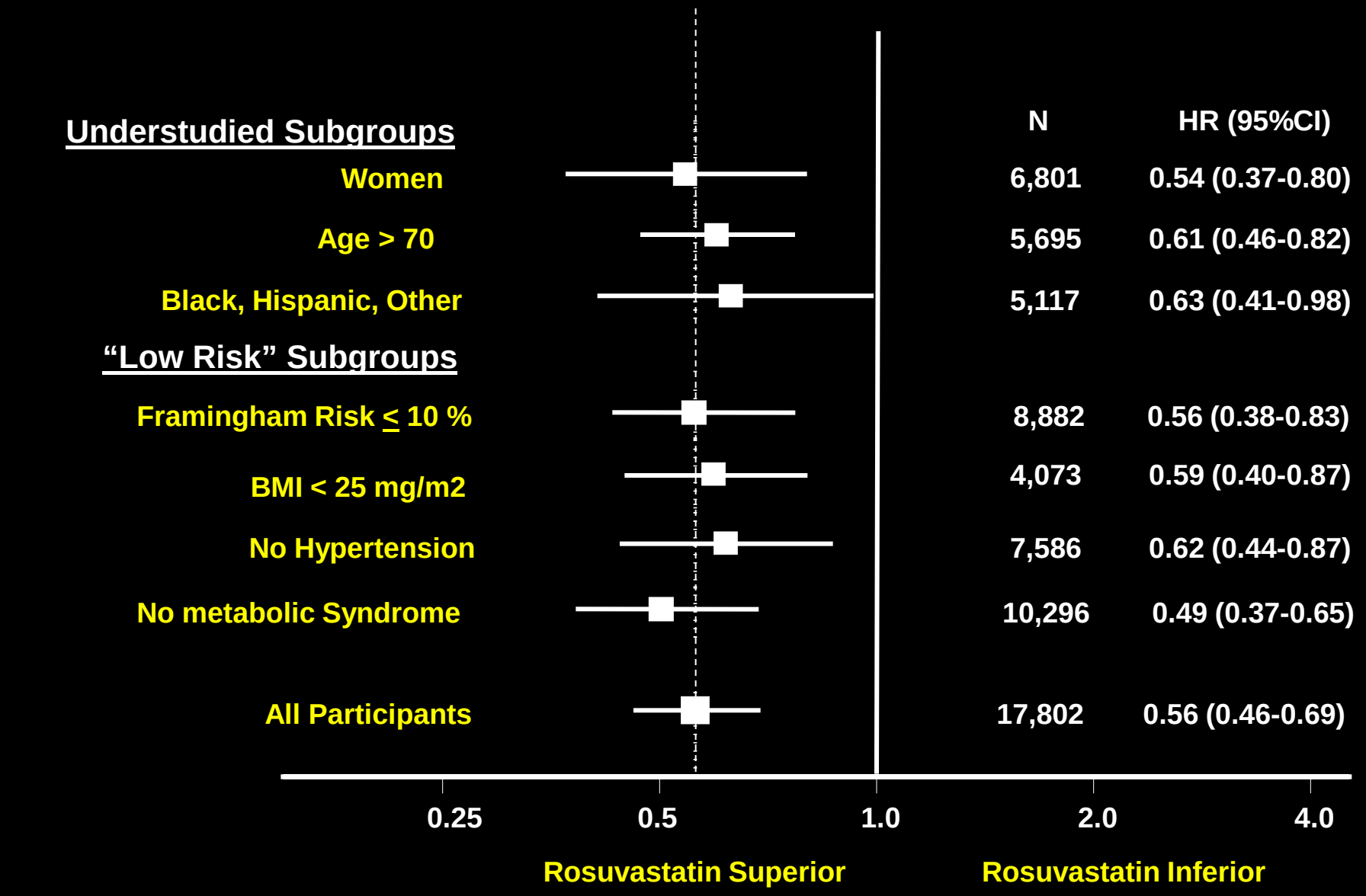


Number at Risk										
Rosuvastatin	8,901	8,847	8,787	6,999	4,312	2,268	1,602	1,192	683	227
Placebo	8,901	8,852	8,775	6,987	4,319	2,295	1,614	1,196	684	246

JUPITER

Ridker et al NEJM 2008;359:2195-2207

Primary Endpoint – Understudied or "Low Risk" Subgroups



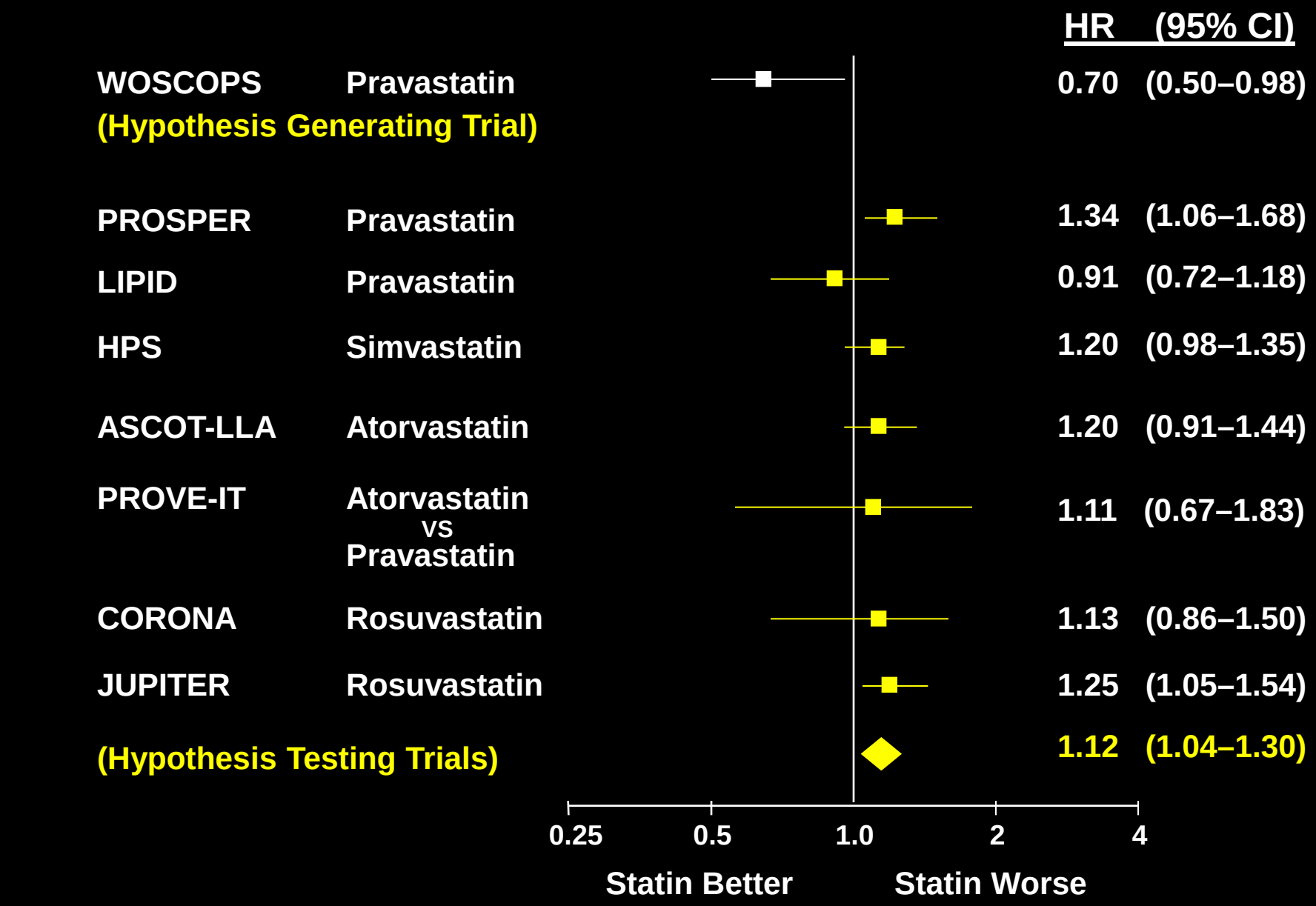
JUPITER
Adverse Events and Measured Safety Parameters

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

*Occurred after trial completion, trauma induced.
**Physician reported

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

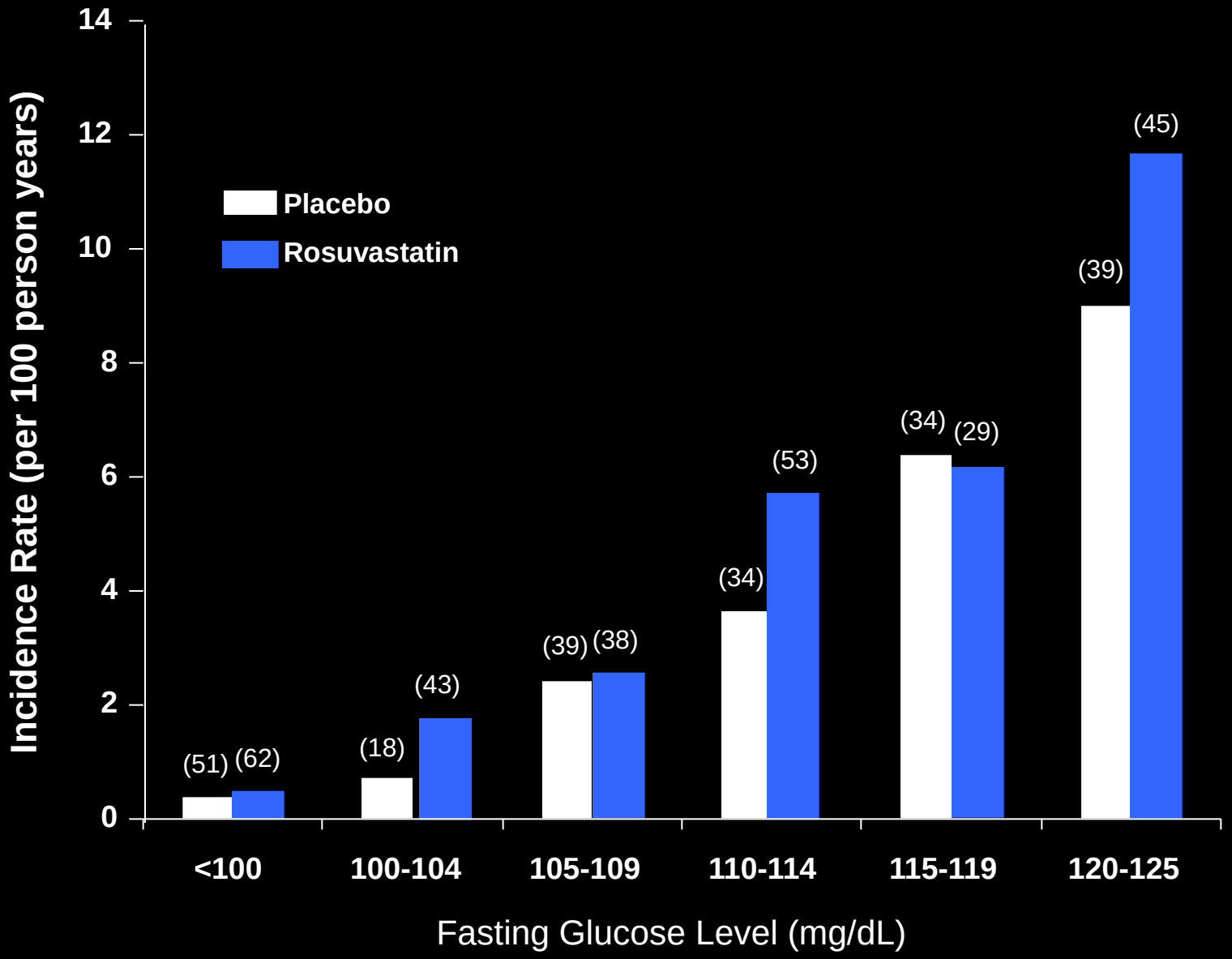
JUPITER
Statins and the Development of Diabetes



JUPITER

Ridker et al Lancet 2012;380:

Incident Diabetes Limited to Those With Impaired Fasting Glucose



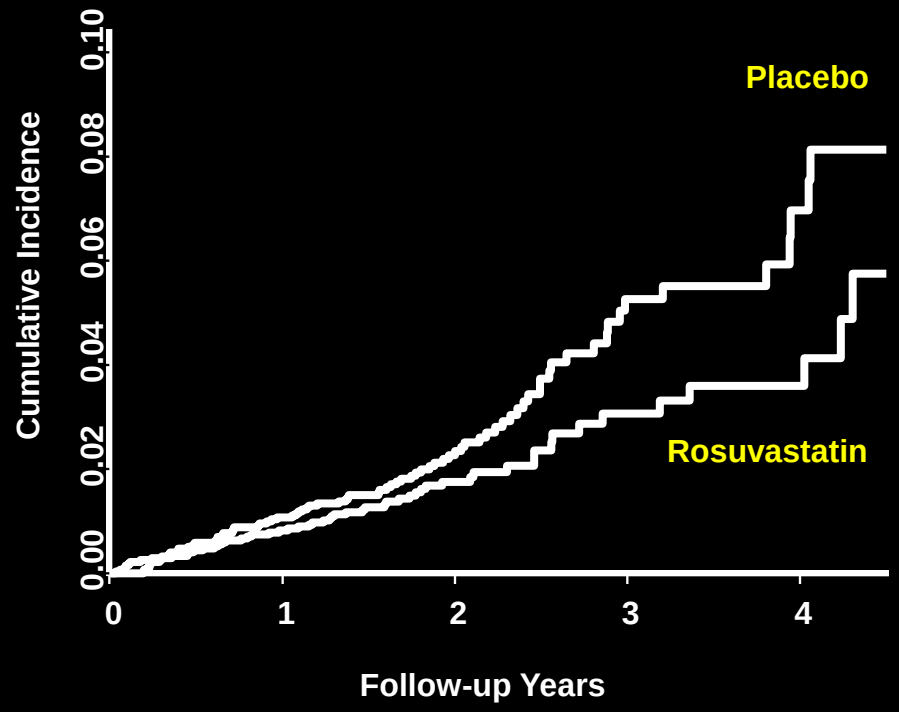
JUPITER

Ridker et al Lancet 2012

Statin Highly Effective in All Patients – Primary Endpoint

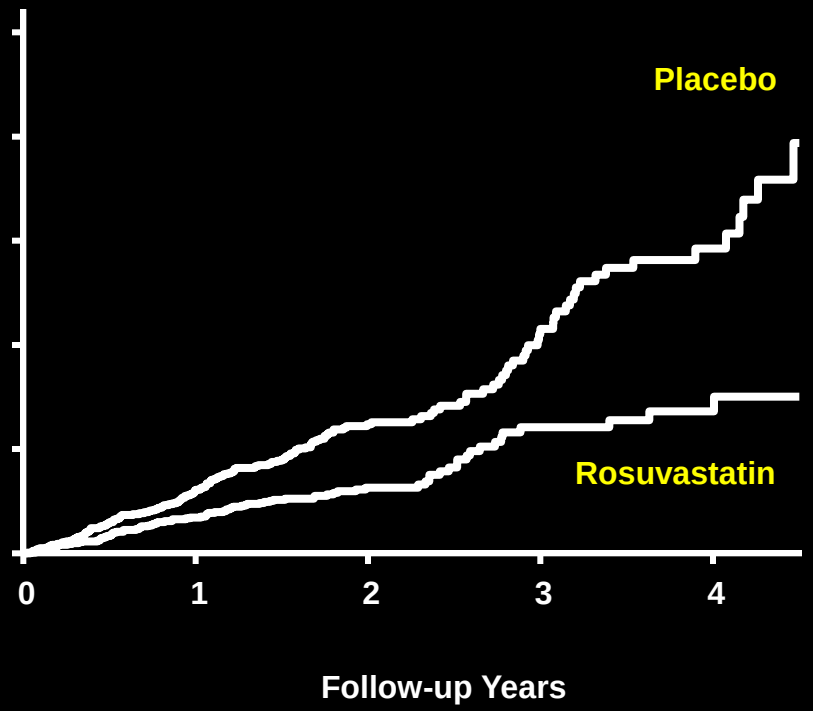
Impaired Fasting Glucose

HR 0.69, 95% CI 0.49-0.98



Normal Fasting Glucose

HR 0.51, 95% CI 0.40-0.67



Cardiovascular Benefits and Diabetes Risks of Statin Therapy in Primary Prevention: The JUPITER Trial

- In absolute terms for those without a major diabetes risk factor, 86 vascular events or death were avoided by statin therapy with no excess cases of diabetes diagnosed.
- In absolute terms for those with a major diabetes risk factor, 134 vascular events or deaths were avoided by statin therapy for every 54 new cases of diabetes diagnosed.
- Statin therapy increased the time to diagnosis of diabetes by 5.4 weeks.
- Conclusion: In primary prevention, the cardiovascular and mortality benefits of statin therapy exceed the diabetes hazard, including among individuals at high risk for developing diabetes. Long-term microvascular effects unknown.

2010 ACC/AHA Guidelines for Assessment of Cardiovascular Risk in Asymptomatic Adults

"The initial step in risk assessment in individual patients involves the ascertainment of a global risk score (Framingham, Reynolds, etc) and the elucidation of a family history of atherosclerotic CVD. These Class I recommendations which are simple and inexpensive determine subsequent strategies to be undertaken"

Reynolds = Framingham + hsCRP + family history

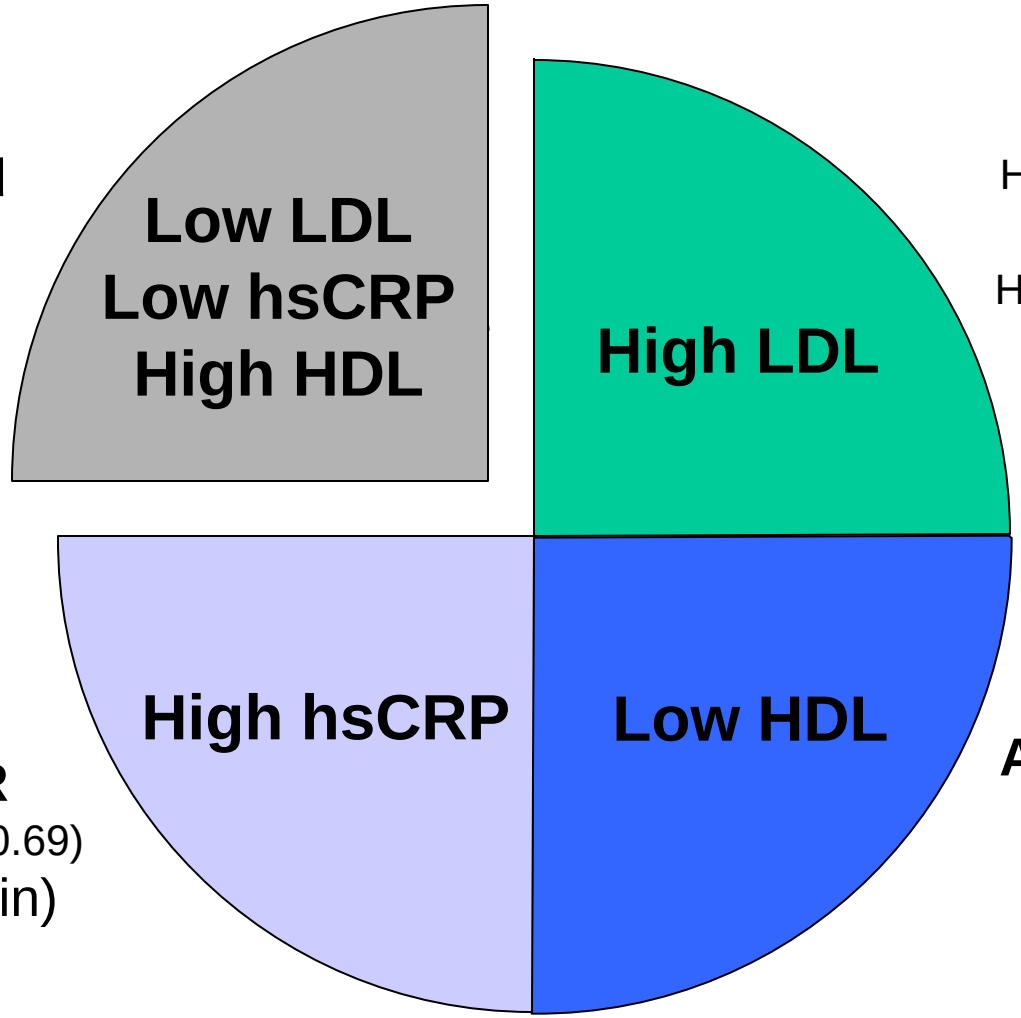
JACC November 16, 2010

2009 Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult

		Primary Goal : LDLC	
High	**CAD, CVA, PVD** **Most pts with Diabetes** **FRS > 20 %** **RRS > 20 %**	**<2mmol/L or 50% reduction**	**Class I** **Level A**
Moderate	**FRS 10- 19 %** **RRS 10-19 %** **LDL > 3.5 mmol/L** **TC/HDLC > 5.0** **hsCRP > 2 in** **men >50 yr** **women > 60 yr**	**<2mmol/L or 50 % reduction**	**Class IIA** **Level A**
Low	**FRS < 10 %**	**<5mmol/L**	**Class IIA** **Level A**

Secondary Targets : TC/HDLC < 4, non HDLC < 3.5 mol/L,
hsCRP < 2 mg/L, TG < 1.7 mol/L, ApoB/A<0.8

Guidelines : Statin Therapy in Primary Prevention
What works and in whom?



Benefit Untested

WOSCOPS
HR 0.70 (0.57-0.84)
MEGA
HR O.67 (0.49-0.91)
(pravastatin)

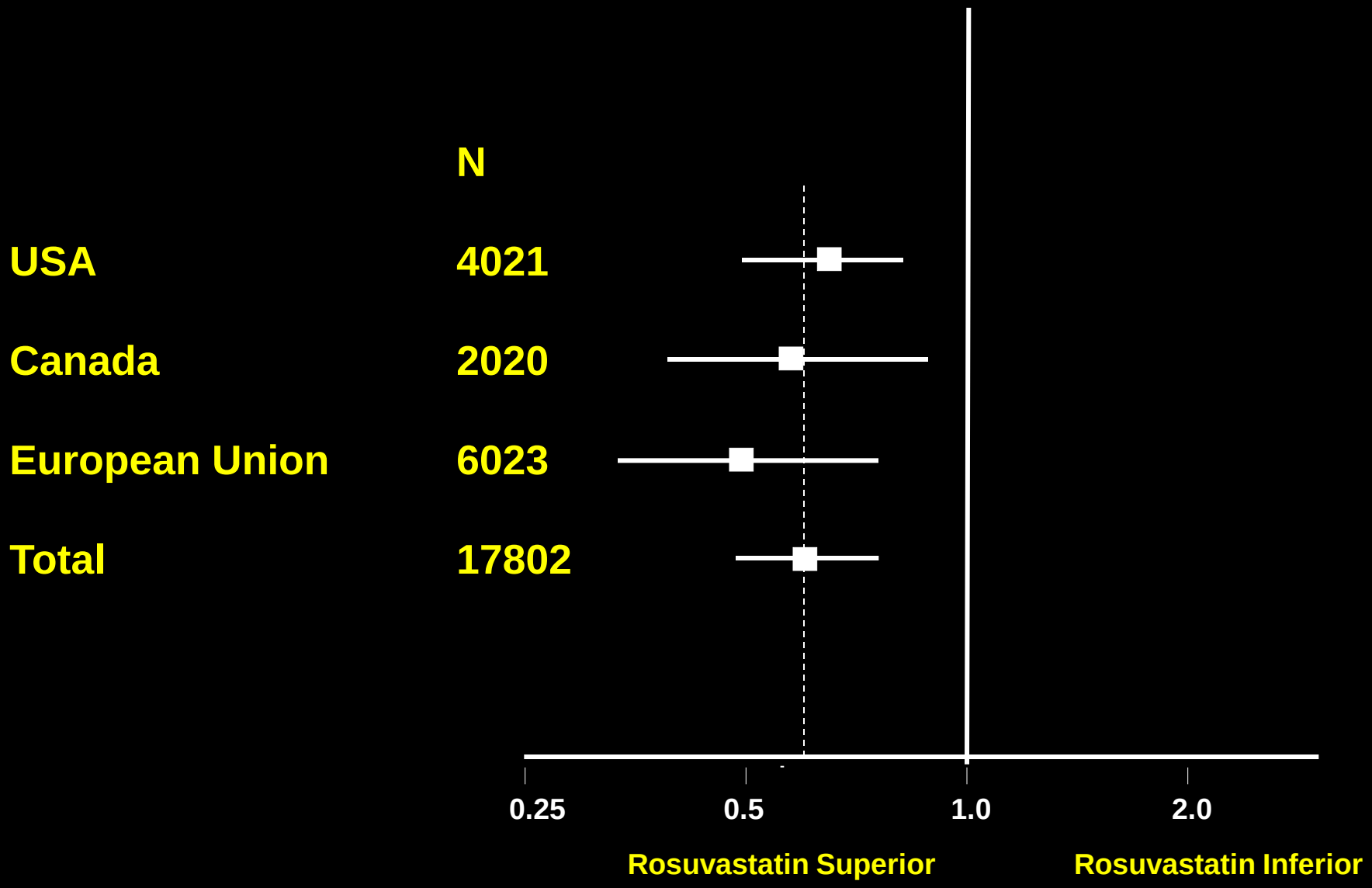
JUPITER
HR 0.56 (0.46-0.69)
(rosuvastatin)

AFCAPS/TexCAPS
HR 0.63 (0.50-0.79)
(lovastatin)

Circ Cardiovasc Qual Outcomes 2012;5:592-3
Eur Heart J 2013;34:1258-61

JUPITER

Consistent Effects in All Geographic Regions, All Pre-Specified Subgroups



European Heart Journal
doi:10.1093/eurheartj/ehs092

JOINT ESC GUIDELINES

European Guidelines on cardiovascular disease prevention in clinical practice (version 2012)

The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)

Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR)†

567 References - No mention of the JUPITER trial, No Change in Practice, No recognition by EMA

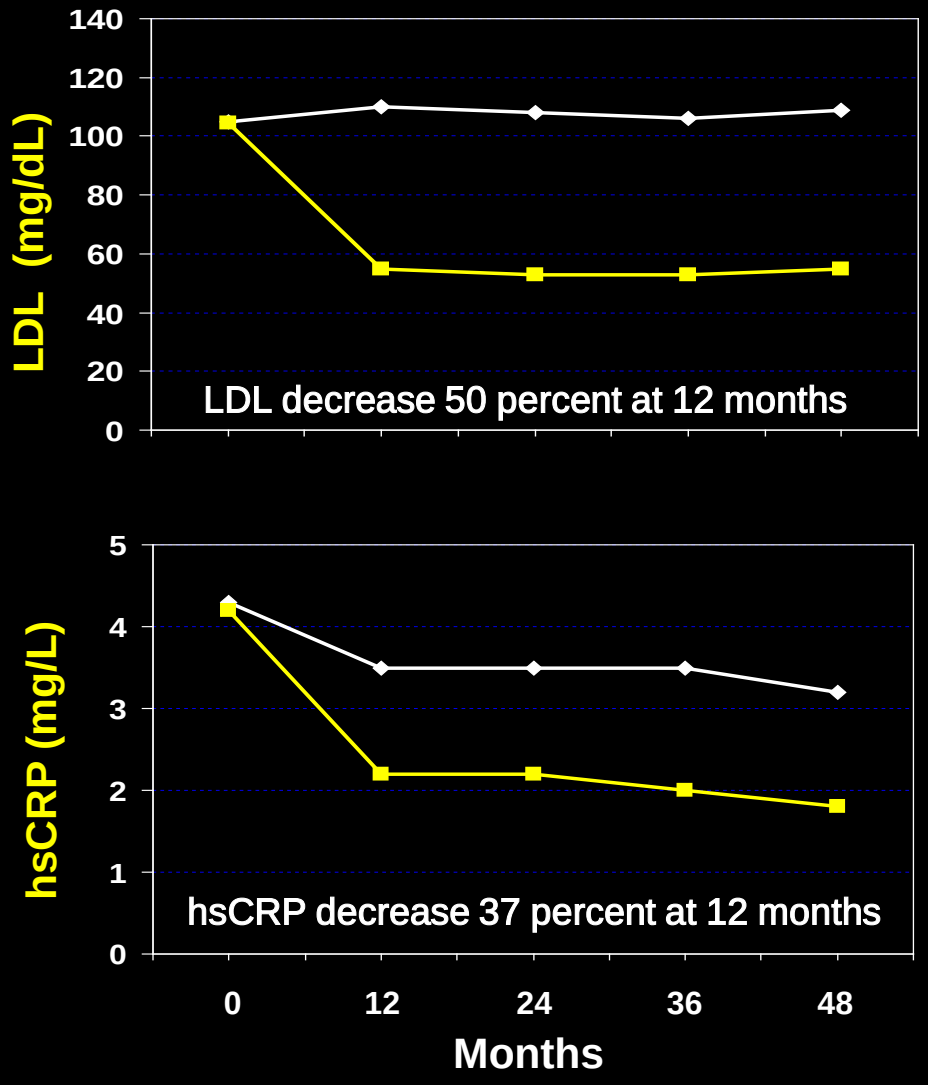
Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions

Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? 1995-2002

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? 2002-2008

Is there evidence that reducing inflammation per se will reduce vascular events? 2009 -

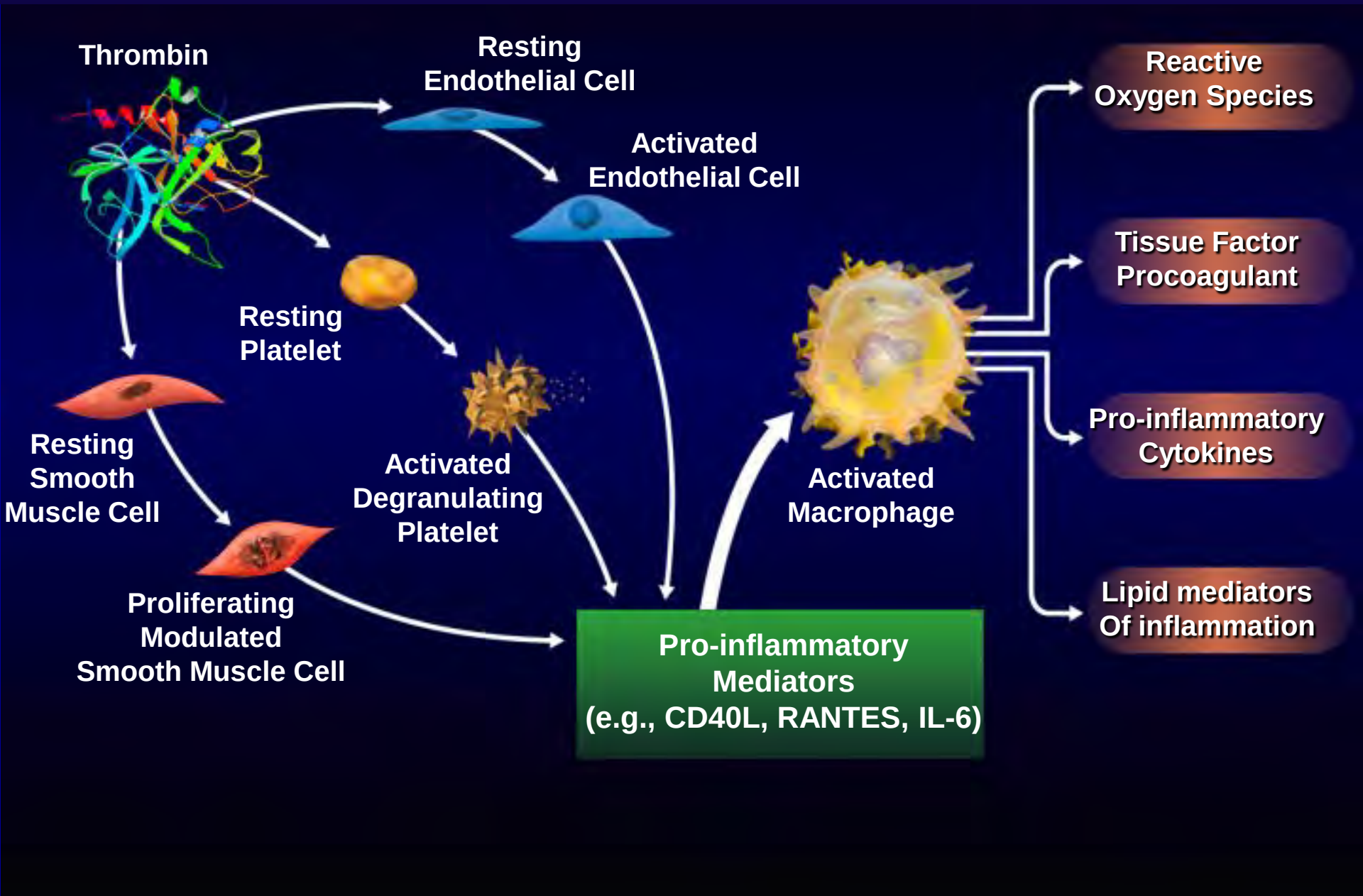
JUPITER
Achieved LDLC, Achieved hsCRP, or Both?



The Real Controversy:

Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?

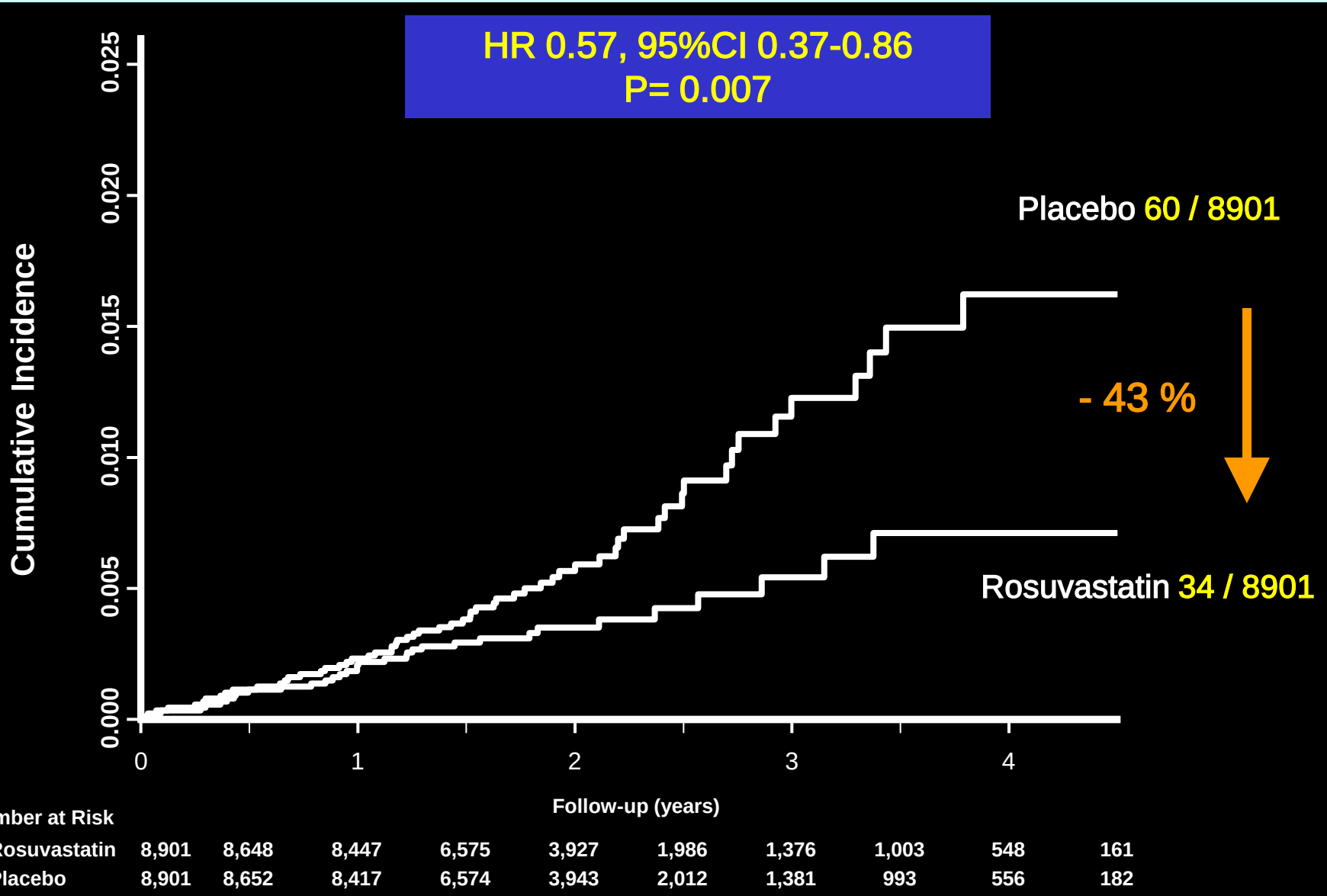
Inflammation and Thrombosis



Venous Endothelium- *transmission electron micrograph*

JUPITER
Total Venous Thromboembolism

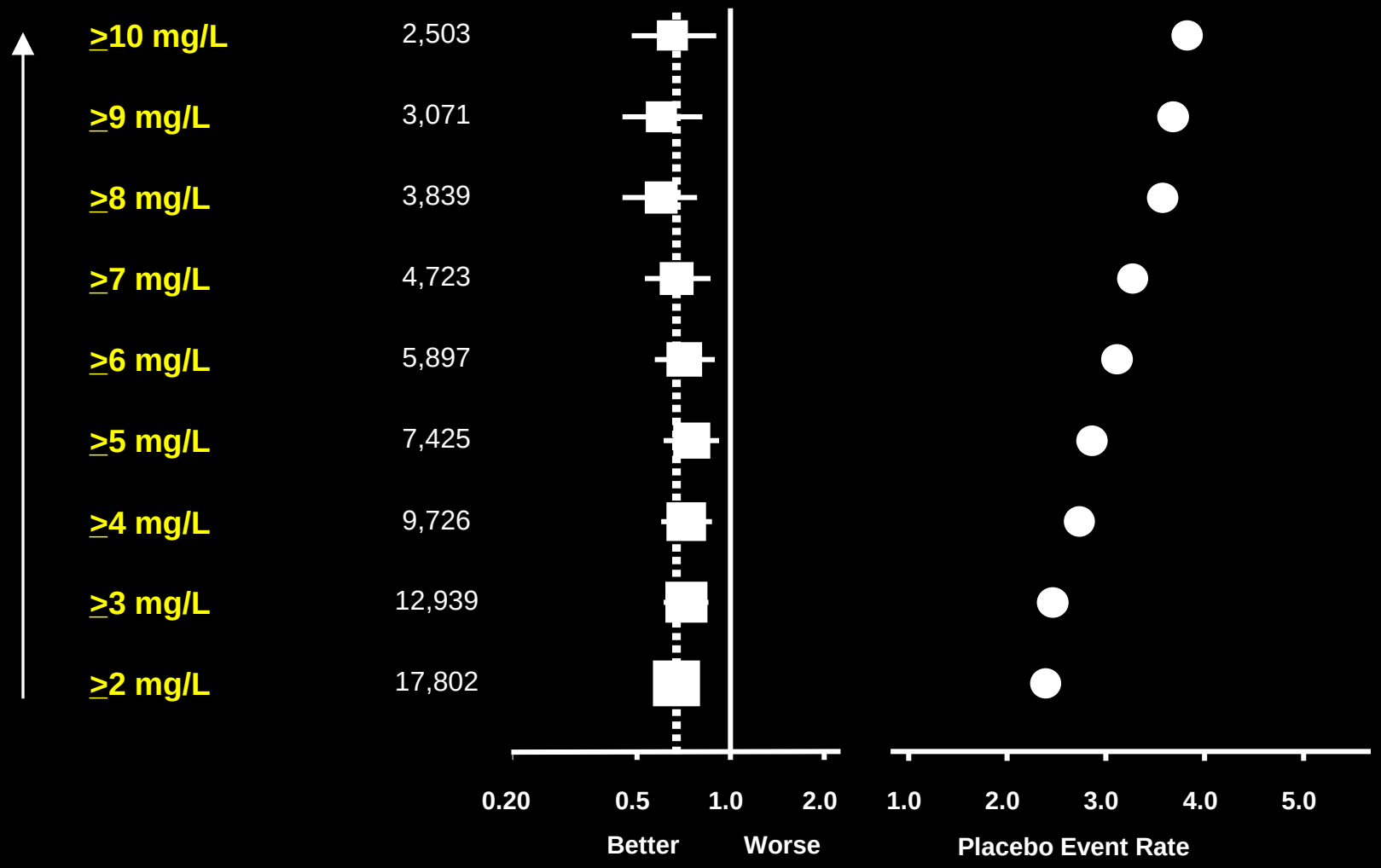
Glynn et al NEJM 2010



JUPITER

Ridker et al, Am J Card 2010;106:206-9

Absolute Risk Reduction Increases With Increasing Levels of hsCRP

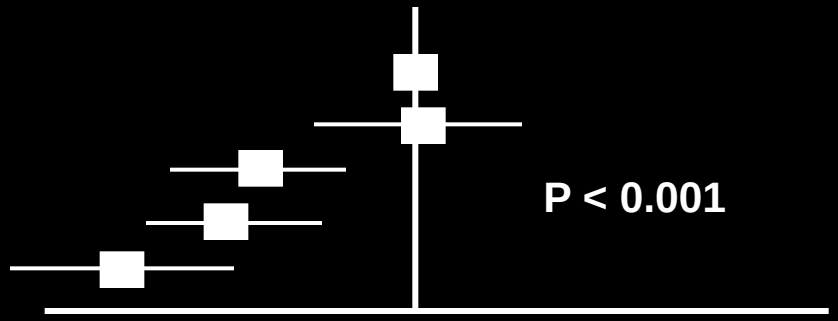


JUPITER

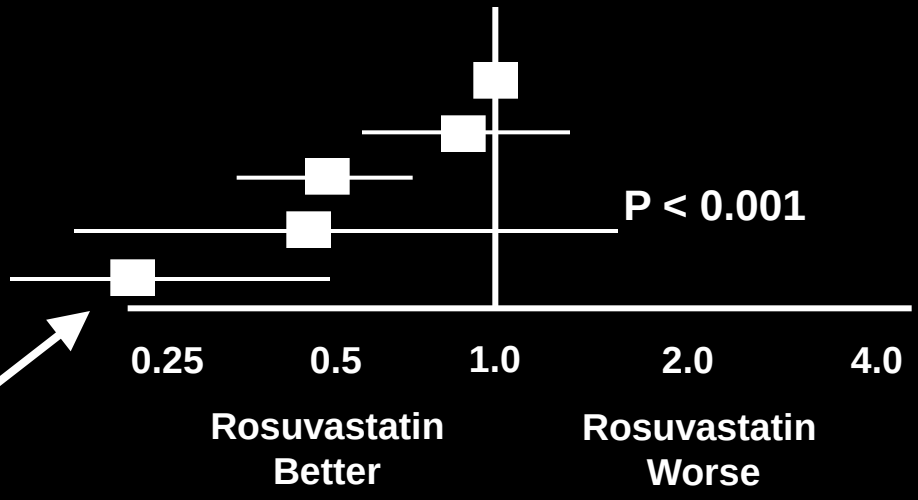
LDL reduction, hsCRP reduction, or both?

Ridker et al Lancet 2009;373:1175-82

	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



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



Full Adjusted Hazard Ratio
0.21, 95% CI 0.09-0.52, P < 0.0001

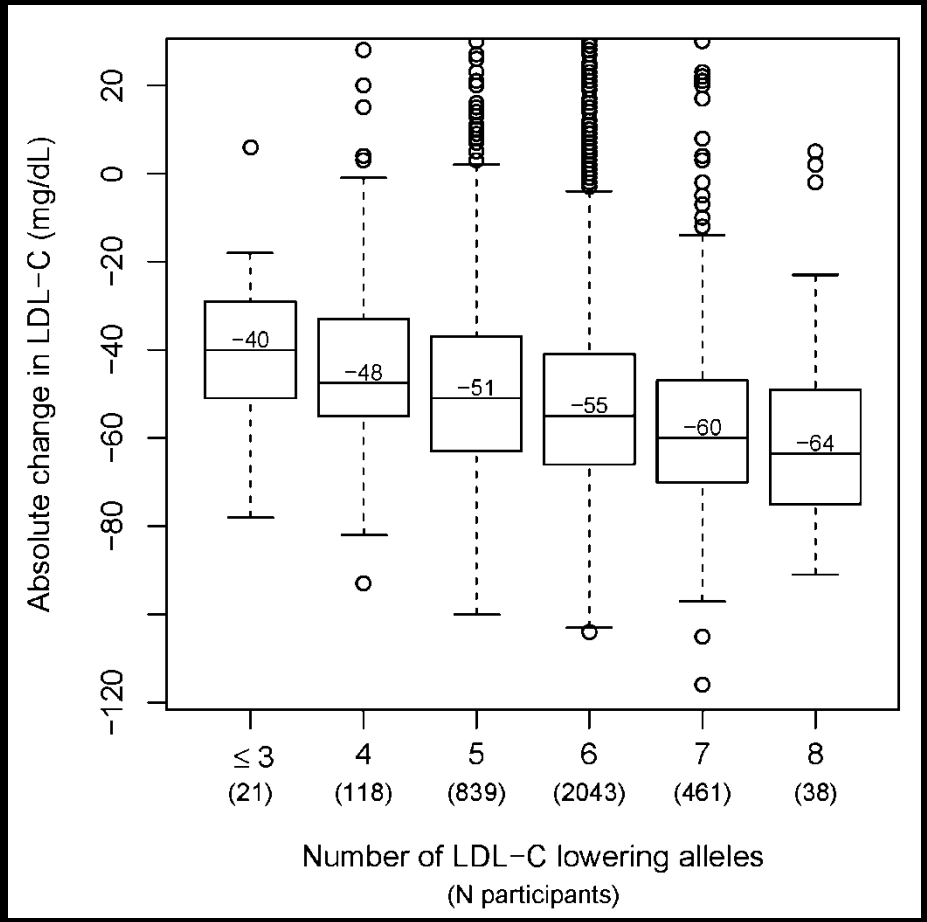
JUPITER

LDL reduction, hsCRP reduction, or both?

JUPITER GWAS:

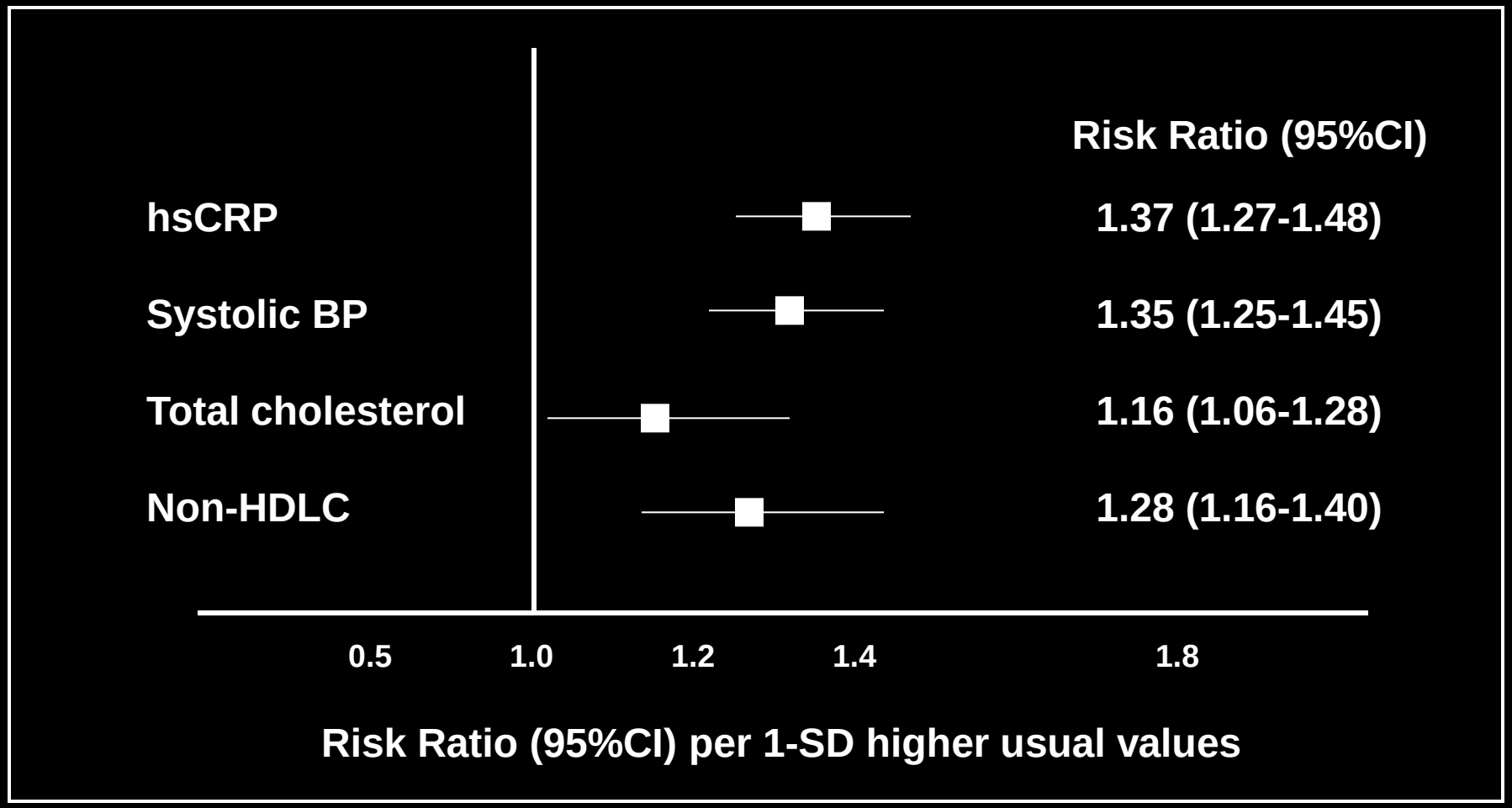
The genetic determinants of rosuvastatin-induced LDL-C reduction do not predict rosuvastatin-induced CRP reduction

The genetic determinants of rousvastatin-induced CRP reduction do not predict rosuvastatin-induced LDL-C reduction



Chasman et al, 2012 Circulation Cardiovascular Genetics
Chu et al, 2012 Circulation Cardiovascular Genetics

Meta-analysis of 54 Prospective Cohort Studies: The magnitude of independent risk associated with inflammation is at least as large, if not larger, than that of BP and cholesterol

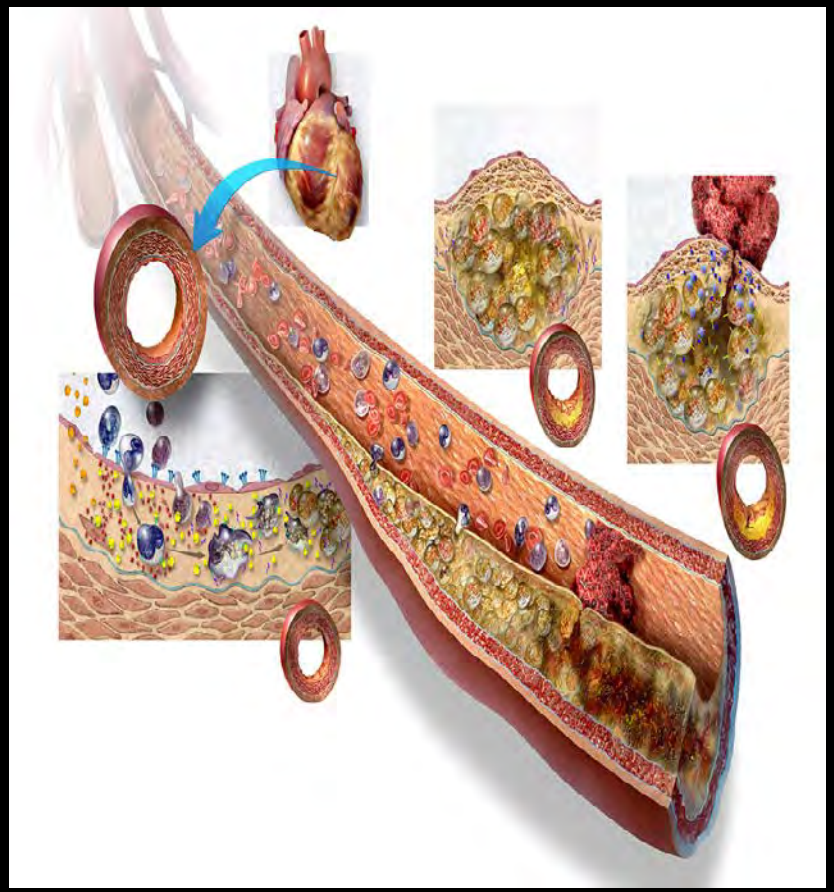


Adjusted for age, gender, smoking, diabetes, BMI, triglycerides, alcohol, lipid levels, and hsCRP

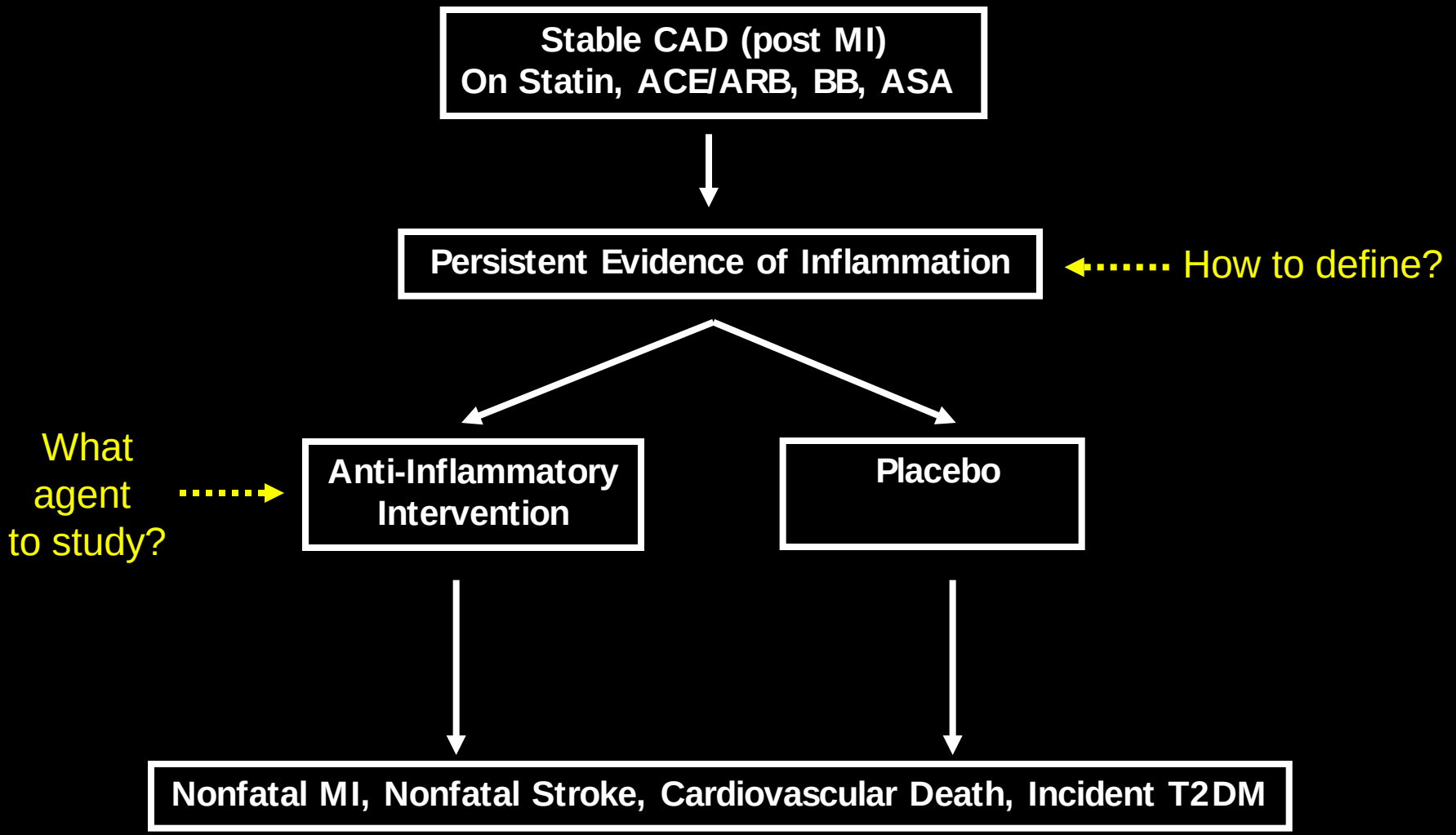
Emerging Risk Factor Collaborators, Lancet January 2010

Can Targeted Anti-Inflammatory Therapy Reduce Cardiovascular Event Rates and Prolong Life?

Testing the Inflammatory Hypothesis of Atherothrombosis: Do we attack the biomarker or attack the process?

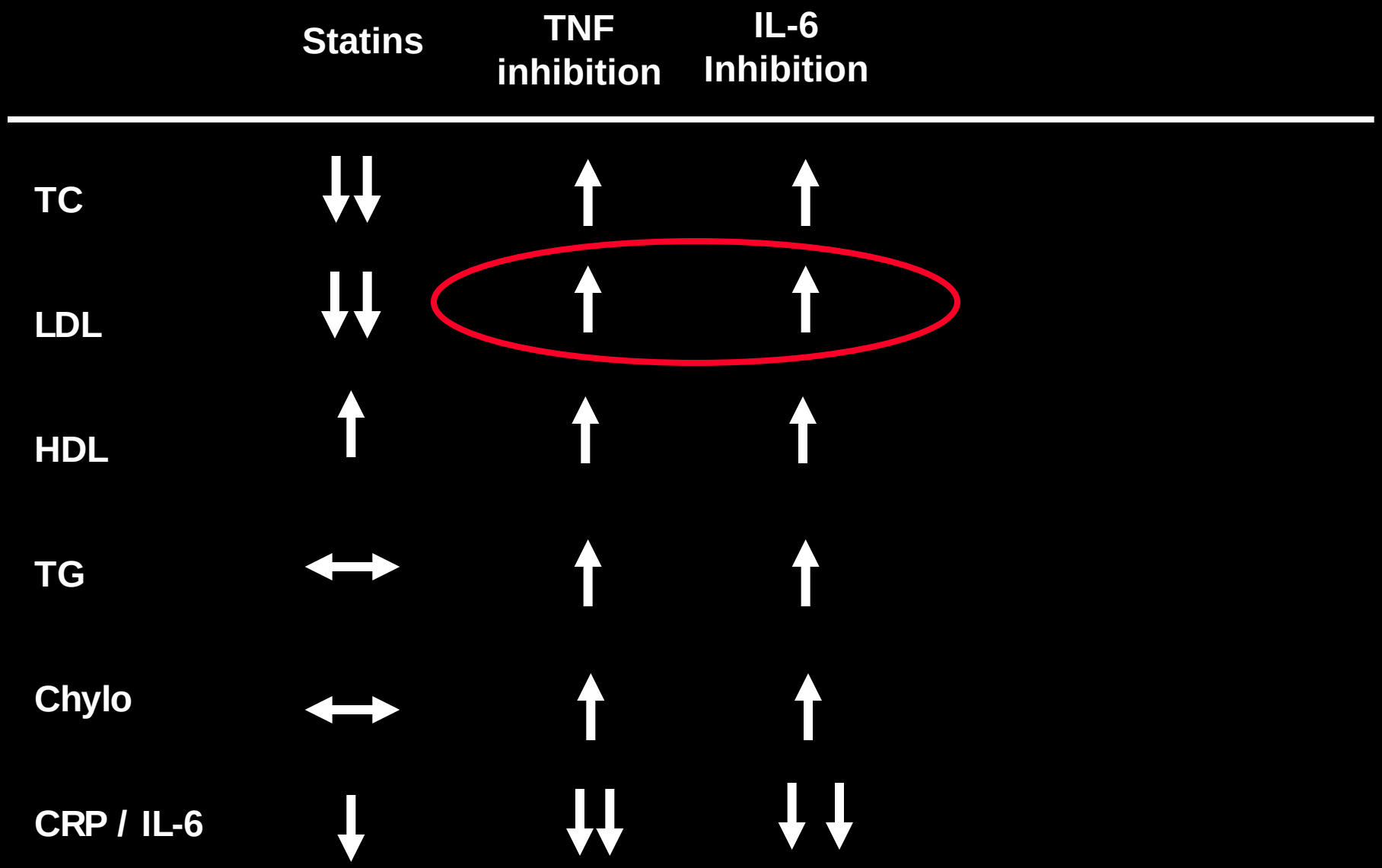


Cardiovascular Inflammation Reduction Trial (CIRT)

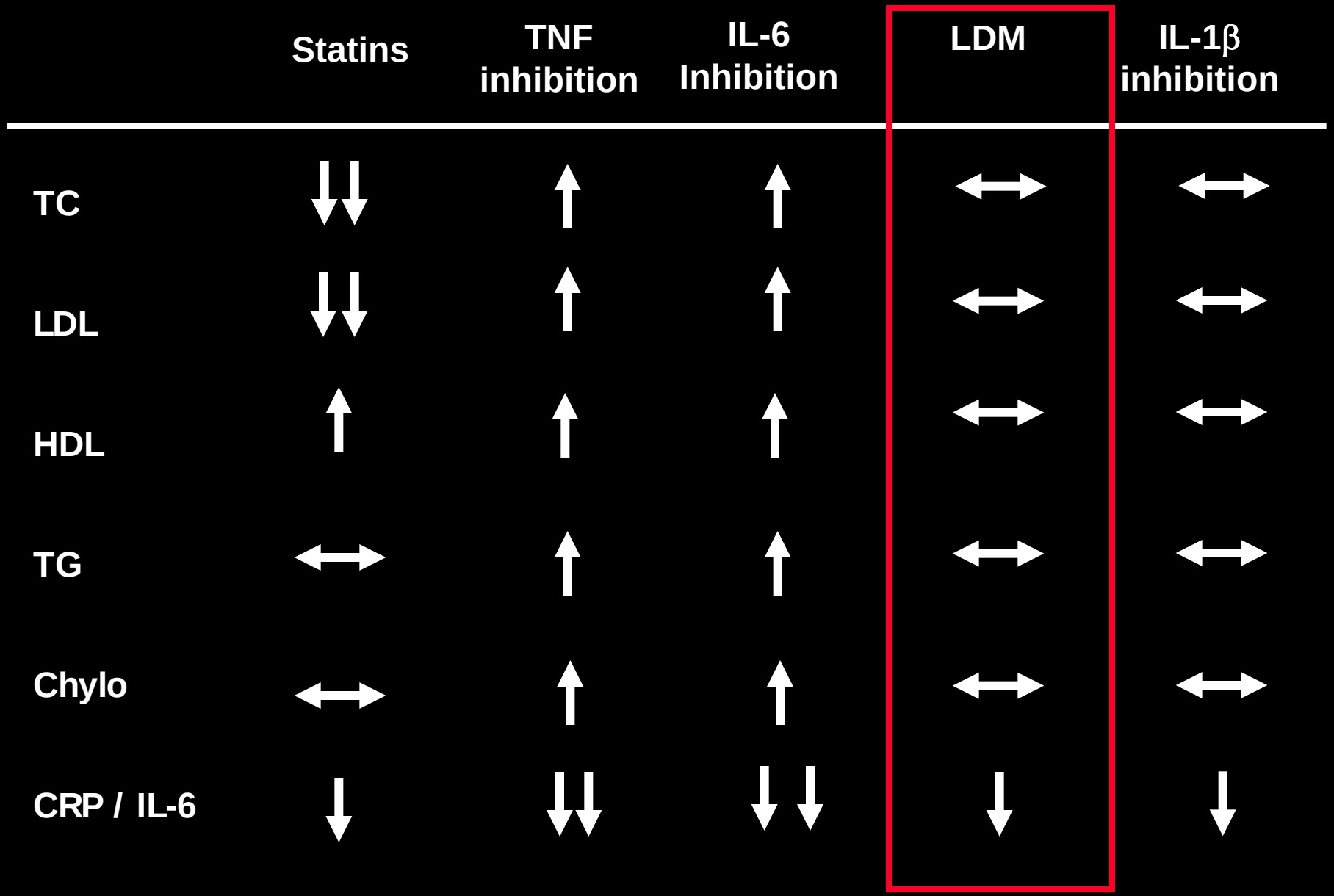


Ridker PM. Thromb Haemost 2009

Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition



Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition



LDM and CVD: Observational Evidence

Cohort	Group	HR*	(95 % CI)	Endpoint	Exposure
Wichita	RA	0.4	(0.2 - 0.8)	Total Mortality	LDM
Choi 2002		0.3	(0.2 - 0.7)	CV Mortality	LDM
		0.4	(0.3 – 0.8)	CV Mortality	LDM < 15 mg/wk
Netherlands	RA	0.3	(0.1 – 0.7)	CVD	LDM only
van Helm 2006		0.2	(0.1 – 0.5)	CVD	LDM + SSZ
		0.2	(0.1 – 1.2)	CVD	LDM + HCQ
		0.2	(0.1 – 0.5)	CVD	LDM + SSZ + HCQ
Miami VA	PsA	0.7	(0.6 – 0.9)	CVD	LDM
Pradanovich 2005		0.5	(0.3 – 0.8)	CVD	LDM < 15 mg/wk
	RA	0.8	(0.7 – 1.0)	CVD	LDM
		0.6	(0.5 – 0.8)	CVD	LDM < 15 mg/wk
CORRONA	RA	0.6	(0.3 – 1.2)	CVD	LDM
Solomon 2008		0.4	(0.2 – 0.8)	CVD	TNF-inhibitor
QUEST-RA	RA	0.85	(0.8 – 0.9)	CVD	LDM
Narango 2008		0.82	(0.7 – 0.9)	MI	LDM
		0.89	(0.8 - 1.0)	Stroke	LDM
UK Norfolk	RA, PsA	0.6	(0.4 – 1.0)	Total Mortality	LDM
2008		0.5	(0.3 – 1.1)	CV Mortality	LDM

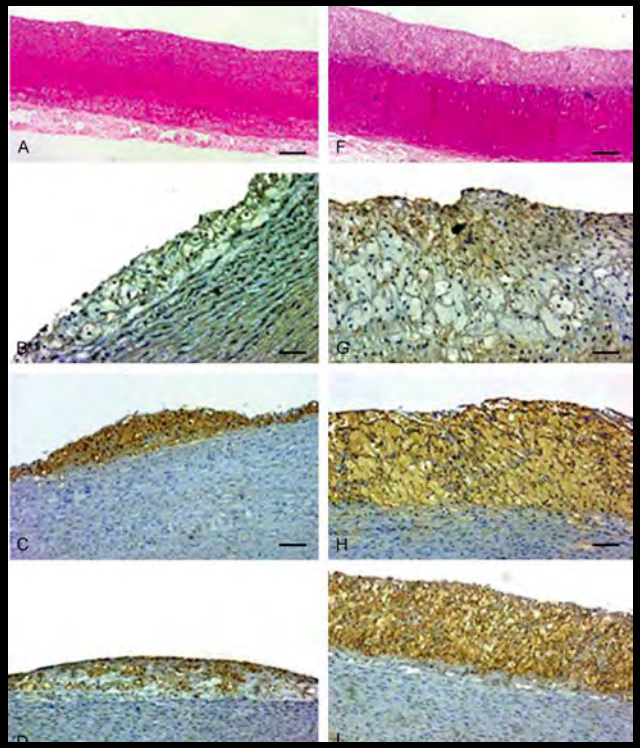
Methotrexate Inhibits Atherogenesis in Cholesterol-fed Rabbits

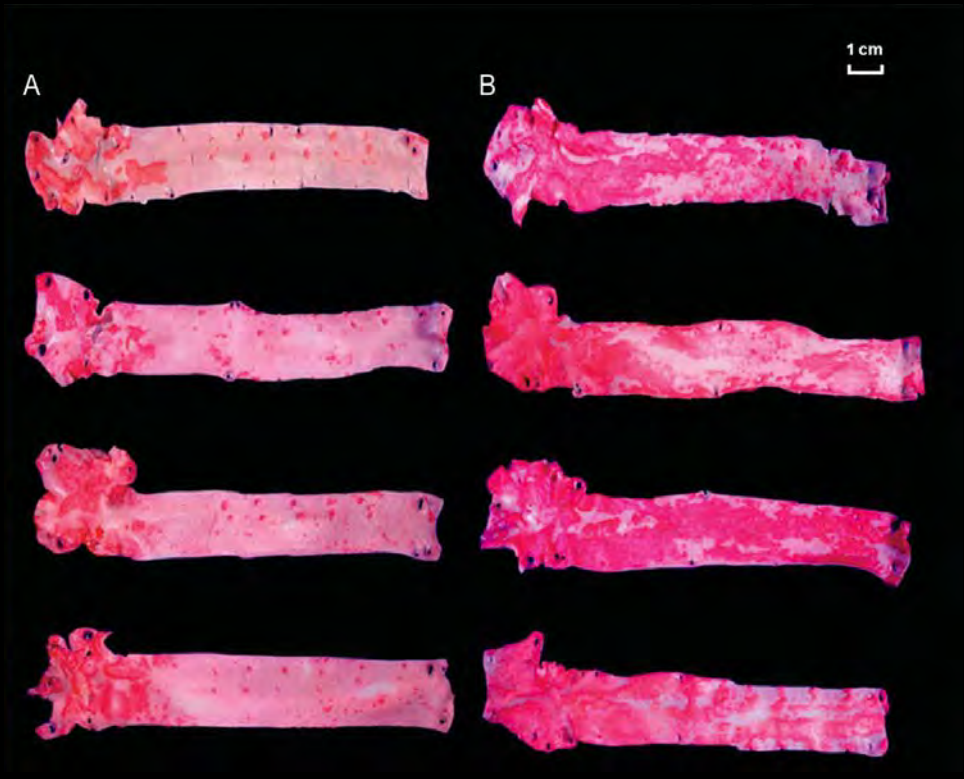
H & E

Anti-VSMC

Anti-rabbit macrophage

Anti-rabbit MMP-9



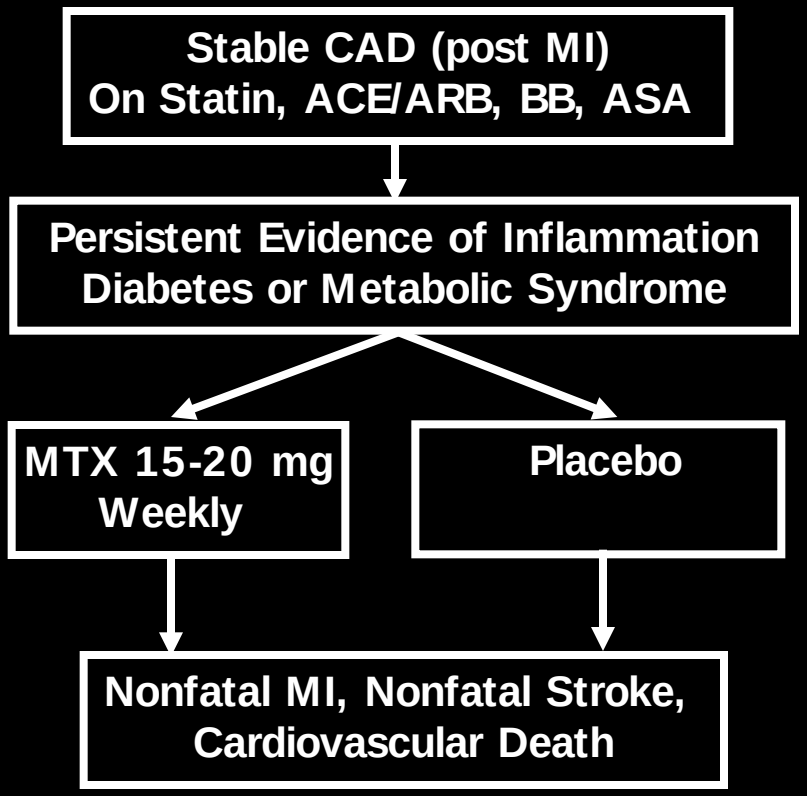


MTX Control MTX Control

Bulgarelli et al, J Cardiovasc Pharmacol 2012;59:308-14

Cardiovascular Inflammation Reduction Trial (CIRT)

Primary Aims



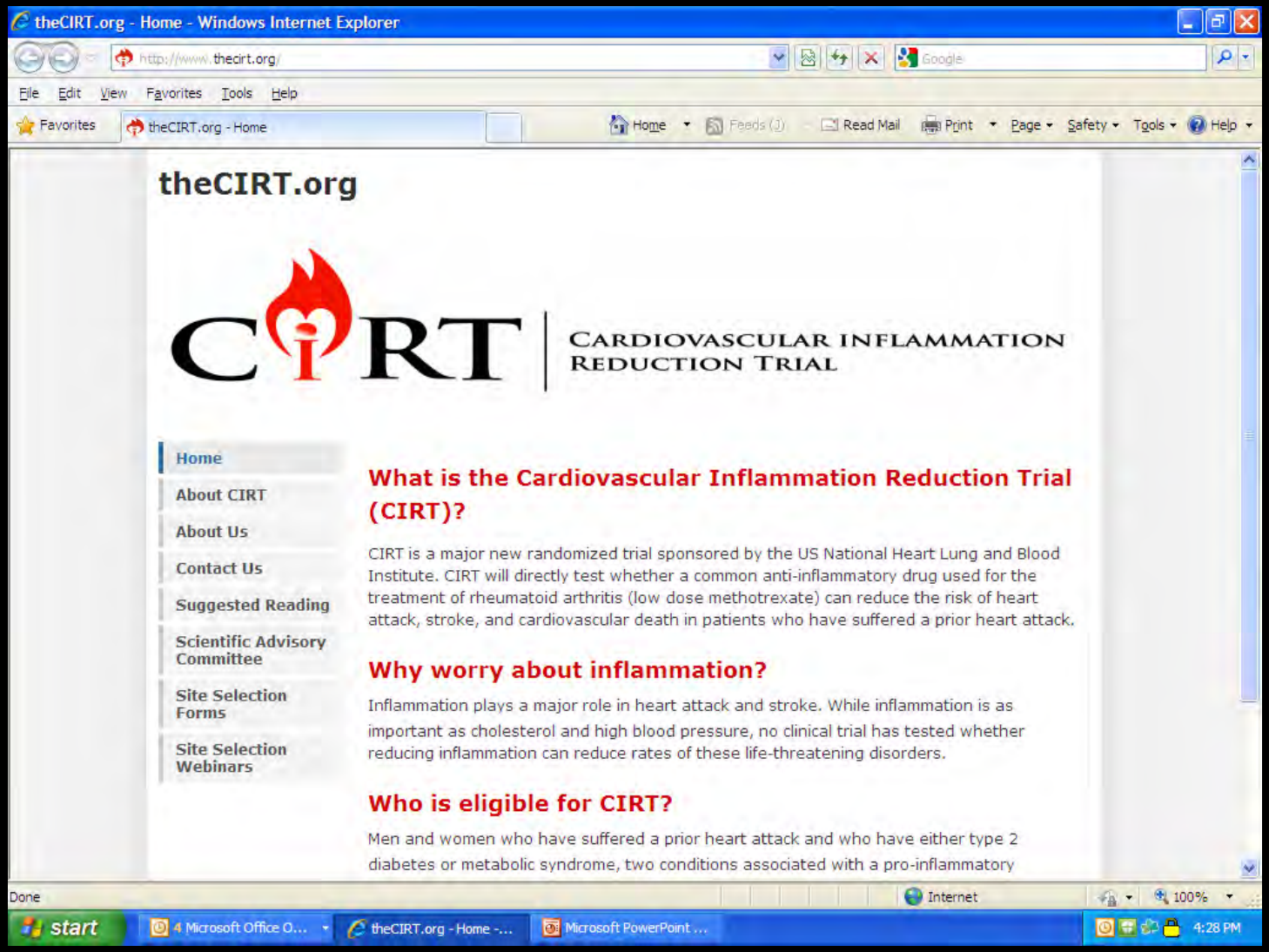
- To directly test the inflammatory hypothesis of atherothrombosis
- To evaluate in a randomized, double-blind, placebo-controlled trial whether MTX given at a target dose of 20 mg po weekly over a three year period will reduce rates of recurrent myocardial infarction, stroke, or cardiovascular death among patients with a prior history of myocardial infarction and either type 2 diabetes or metabolic syndrome.

CIRT | CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

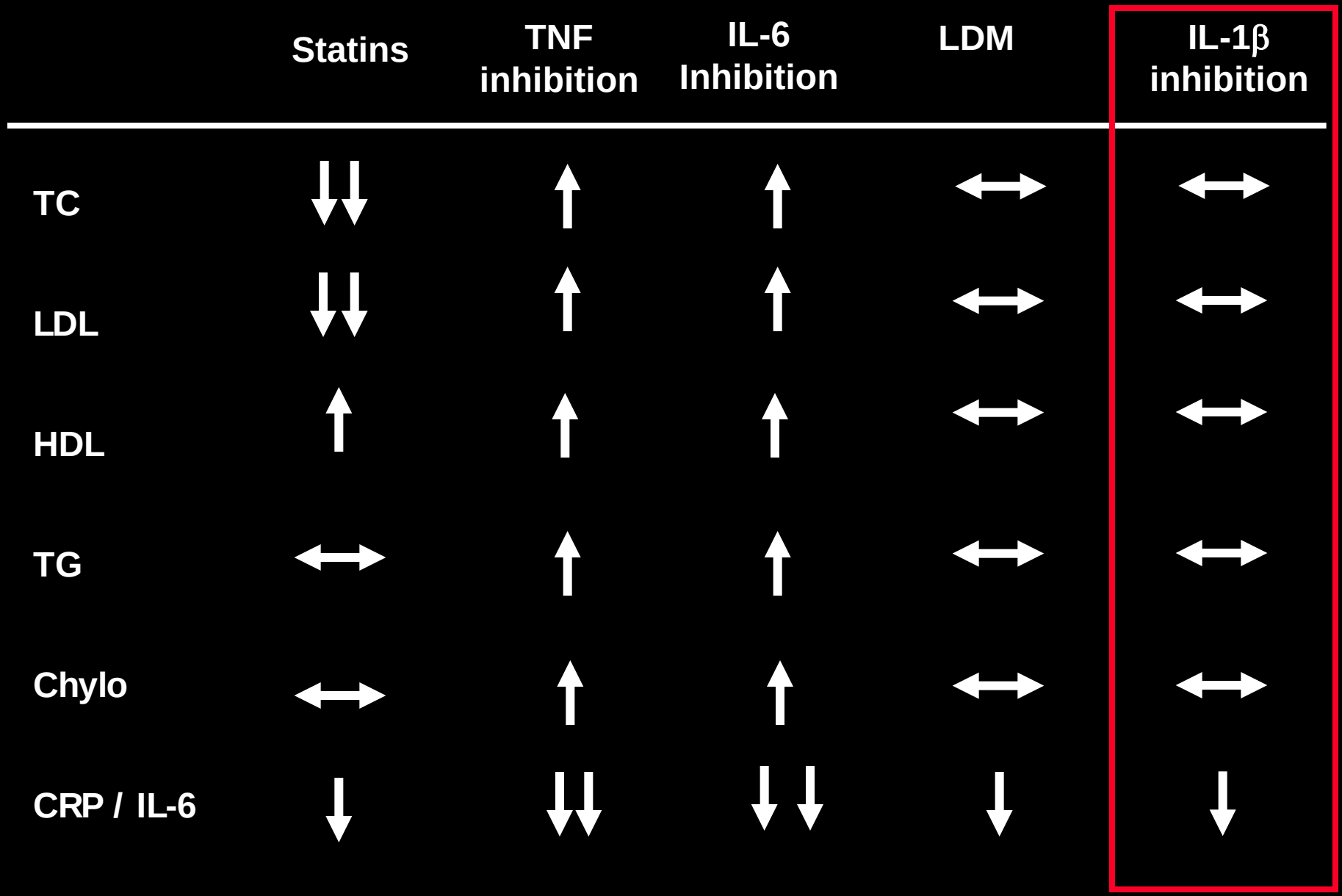
N = 7,000 NHLBI-Sponsored
Enrollment to Start March 2013
350 US and Canadian Sites

Cardiovascular Inflammation Reduction Trial (CIRT)

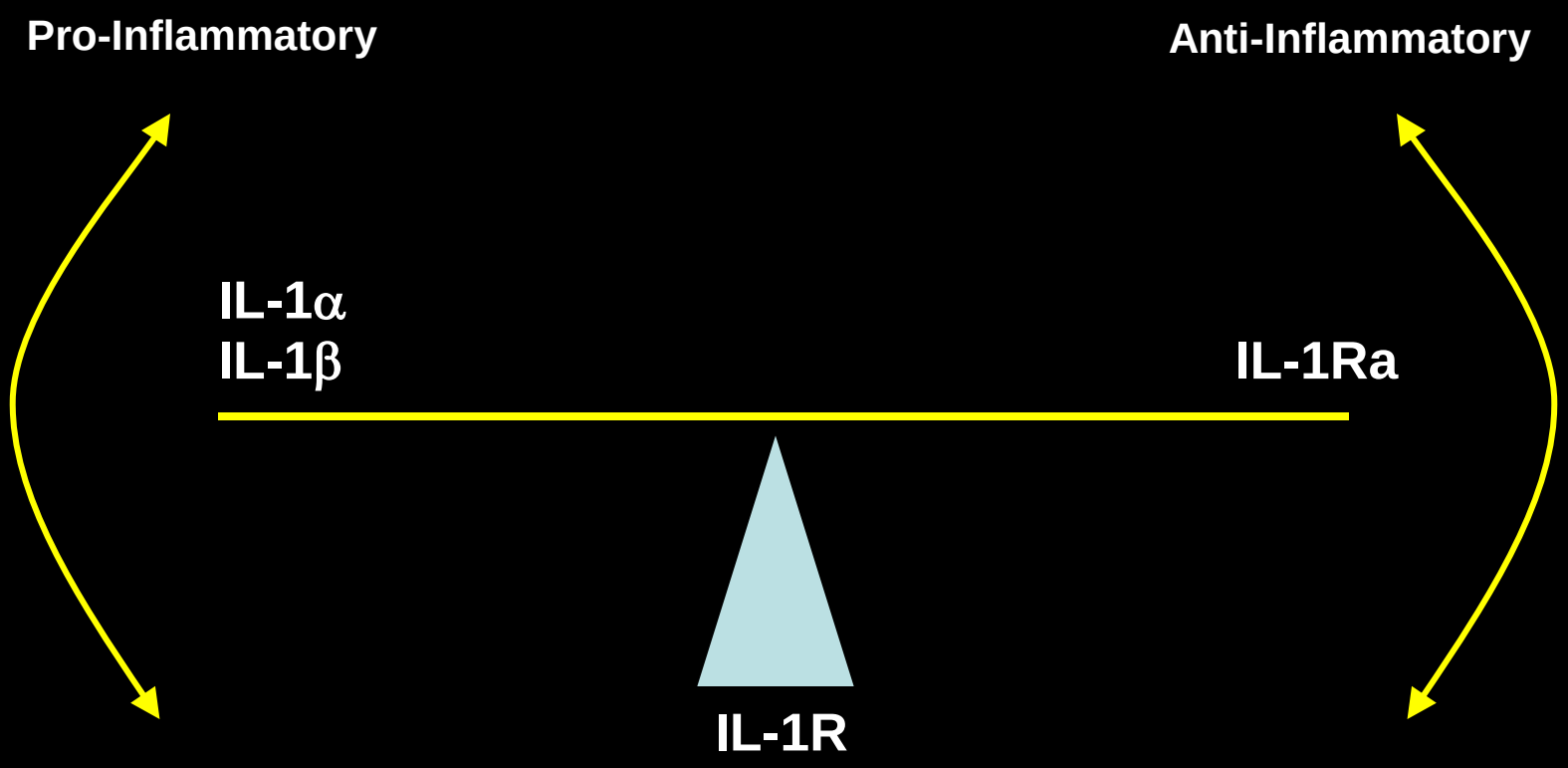
Forms, Updates, and More Information – theCIRT.org website



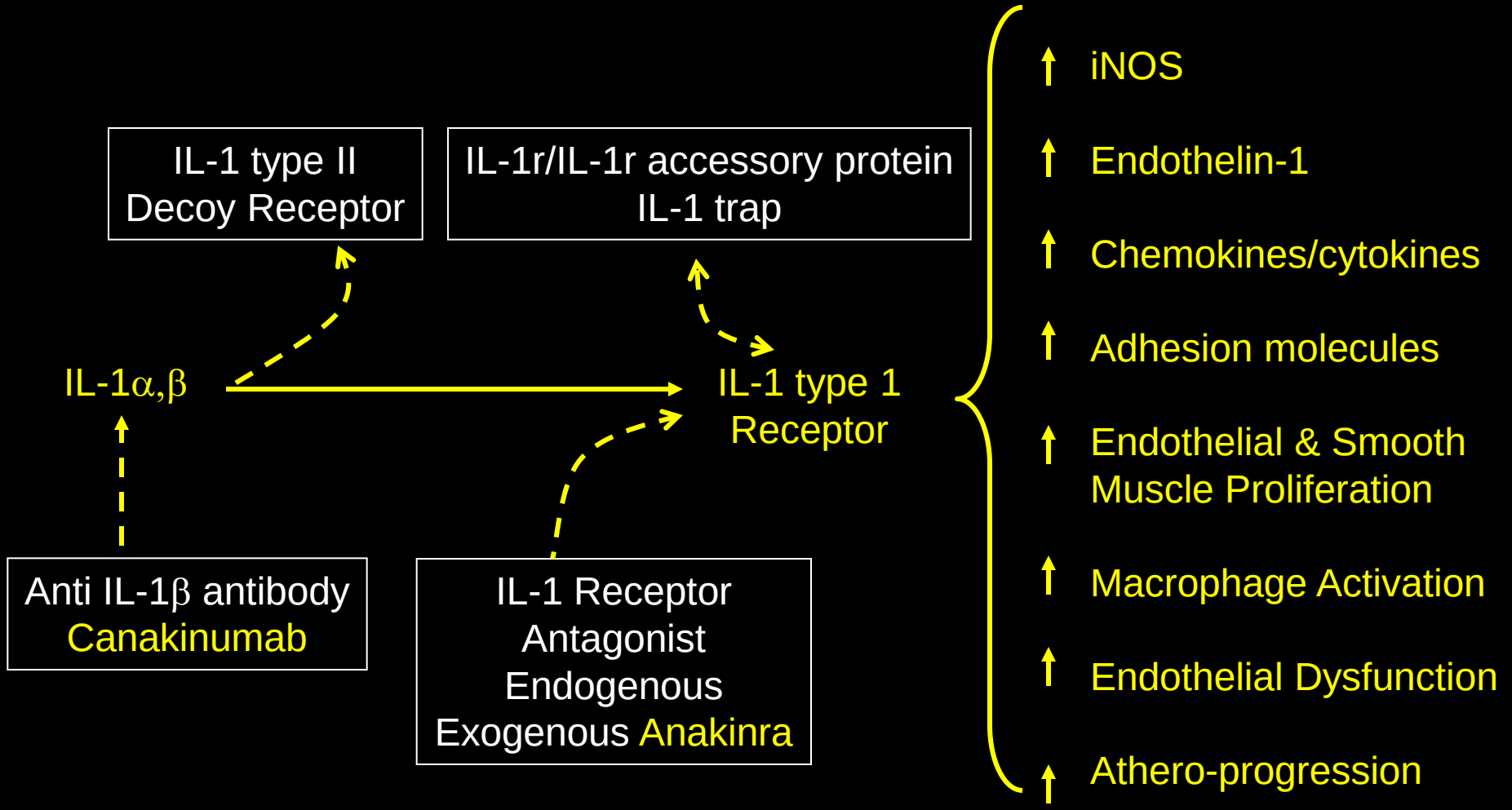
Issues in the Selection of Anti-inflammatory Agents for Trials of Cardiovascular Inflammation Inhibition



The Balance of IL-1 and IL-1Ra : Key Regulatory Proteins for Innate Immunity



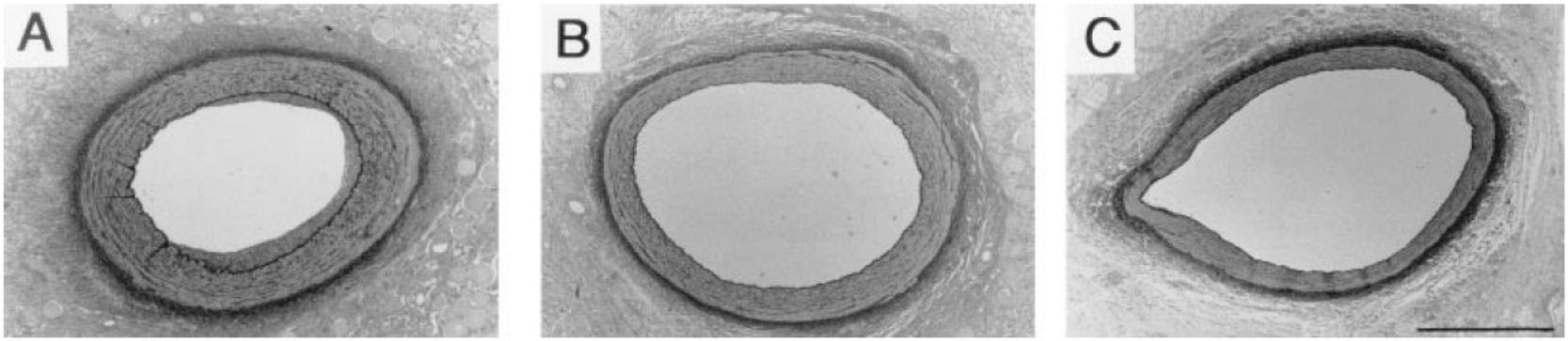
IL-1: Potential Roles in Atherogenesis and Methods of Inhibition



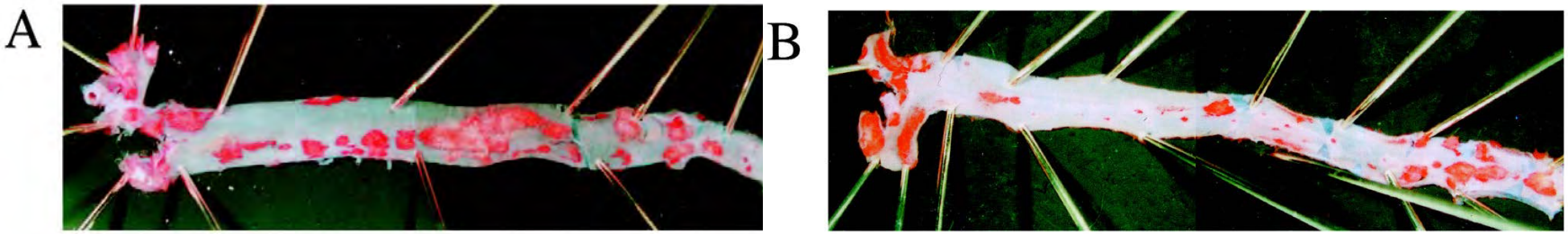
Adapted from Fearon W, Fearon D. Circulation 2008;117:2577-9

Application of IL-1β promotes arterial intimal thickening in porcine coronary artery

Shimokawa et al. (1996) J Clin Invest 97:769



Lack of IL-1β decreases severity of atherosclerosis in ApoE-deficient mice

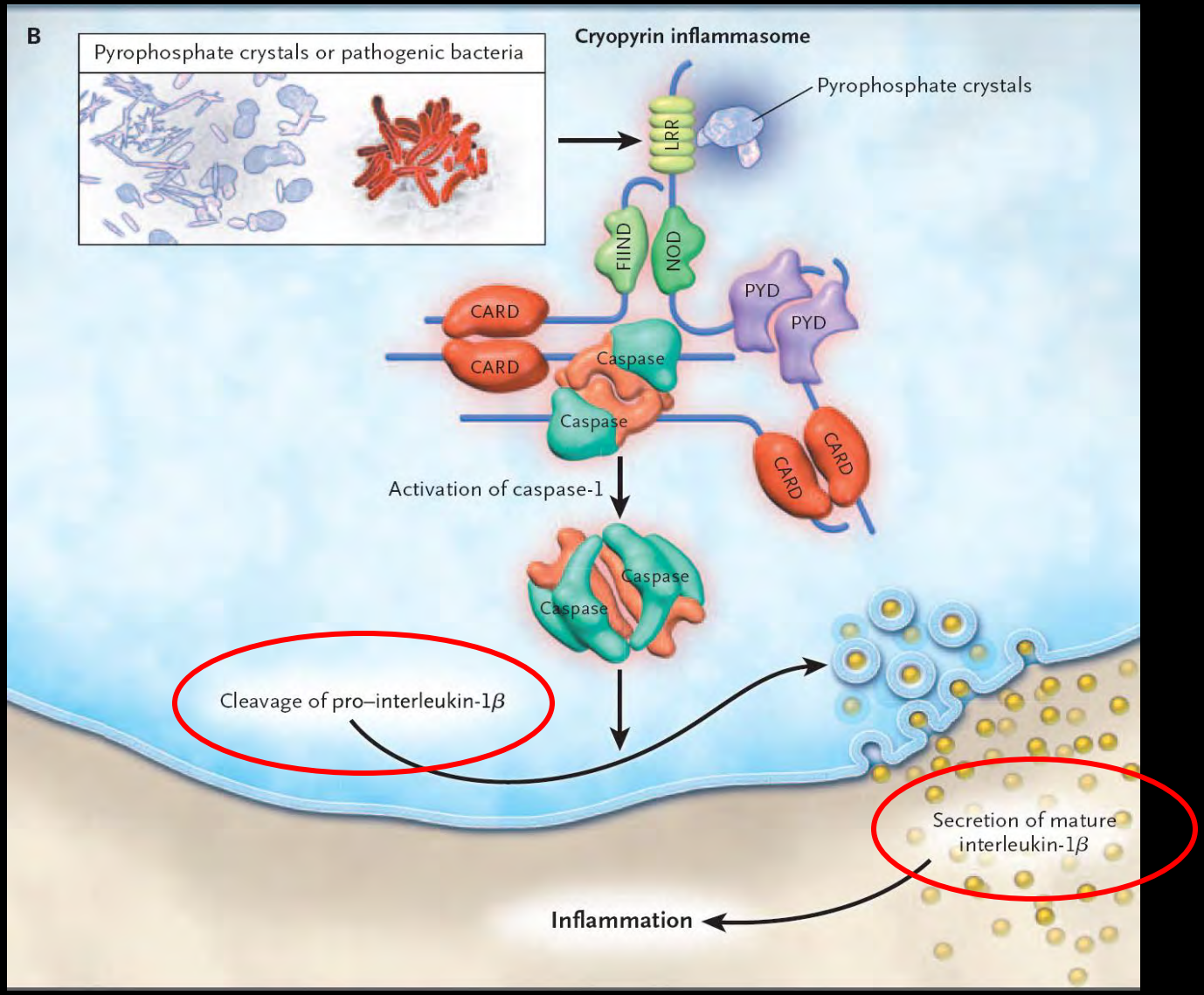


ApoE KO

ApoE KO, IL-1β KO

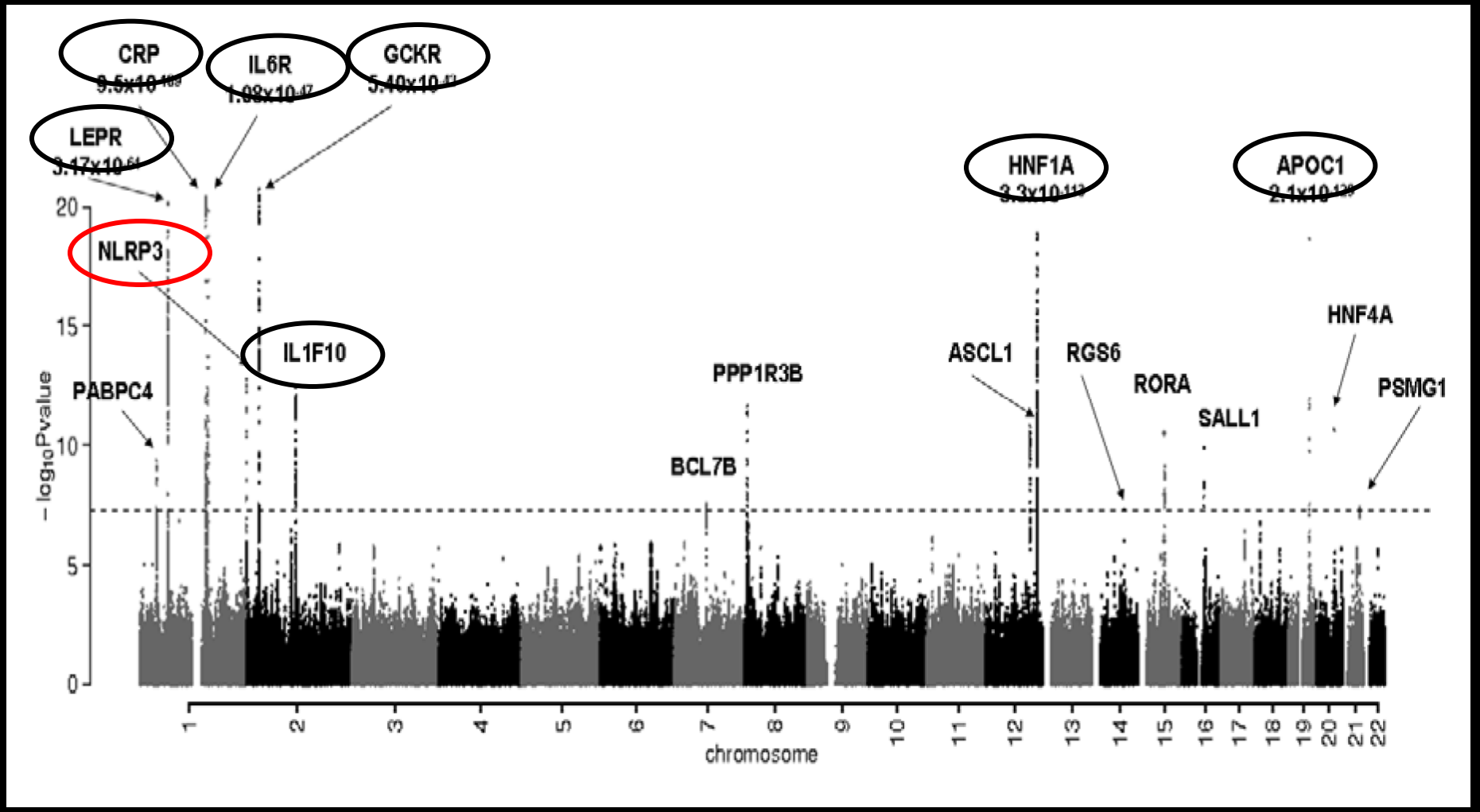
Kirii et al. (2003) Arterioscler Thromb Vasc Biol 23:656

NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1*B* Maturation Endogenous Danger Signals in Vascular Biology?



Drenth JPH, et al, NEJM 2006; 355:730-732

Genetic Determinants of Plasma CRP Level

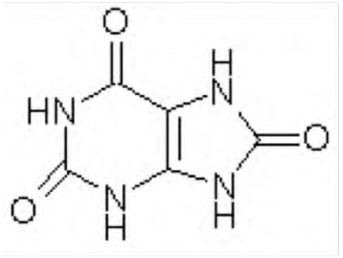


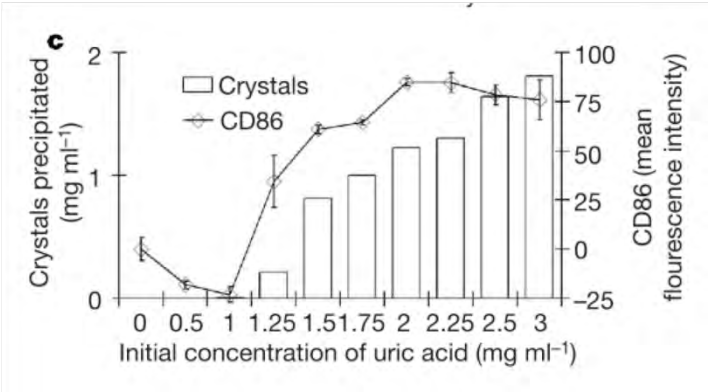
Dehgman et al, Circulation 2011;123:731-8

Phase transition from soluble to crystalline as an endogenous “danger signal”

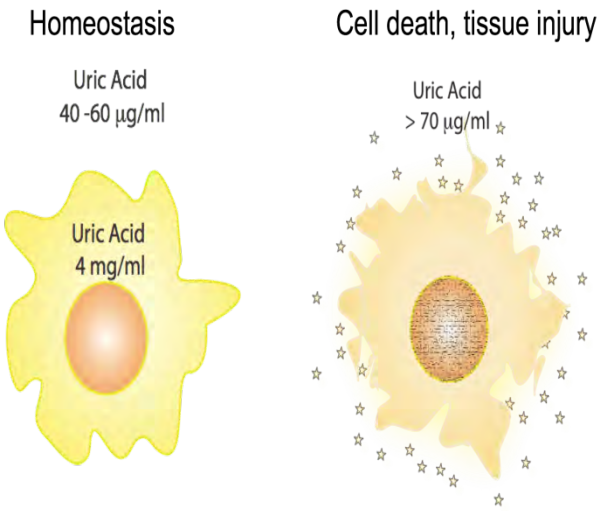
Molecular identification of a danger signal that alerts the immune system to dying cells

Yan Shi[1], James E. Evans[2] & Kenneth L. Rock[1]





Phase transition from soluble to crystalline is a “danger” signal



Crystals activate the NLRP3 inflammasome

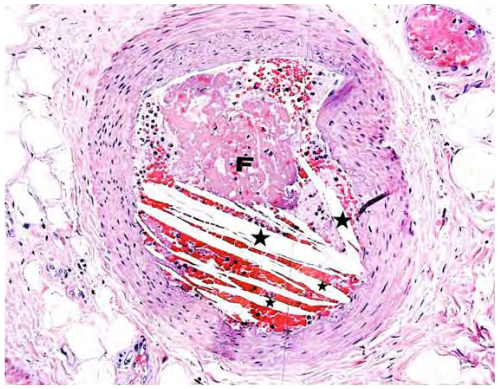
exogenous particles

Alum

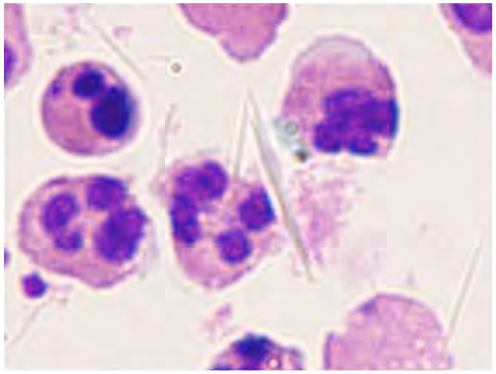
Silica

Asbestos

endogenous material



Cholesterol



Uric acid

Courtesy Eicke Latz Phase transition from soluble to crystalline as a “danger signal”

Vol 464|29 April 2010|doi:10.1038/nature08938 nature

Duewell, P, et al, Nature 2010; 464:1357-1362

LETTERS

NLRP3 inflammasomes are required for atherogenesis and activated by cholesterol crystals

Peter Duewell[1,3]*, Hajime Kono[2]*, Katey J. Rayner[4,5], Cherilyn M. Sirois[1], Gregory Vladimer[1], Franz G. Bauernfeind[6], George S. Abela[8], Luigi Franchi[9], Gabriel Nuñez[9], Max Schnurr[3], Terje Espevik[10], Egil Lien[1], Katherine A. Fitzgerald[1], Kenneth L. Rock[2], Kathryn J. Moore[4,5], Samuel D. Wright[11], Veit Hornung[5]* & Eicke Latz[1,7,10]*

OPEN ACCESS Freely available online

Rajamaki K et al, PLoS One 2010;5:e11765

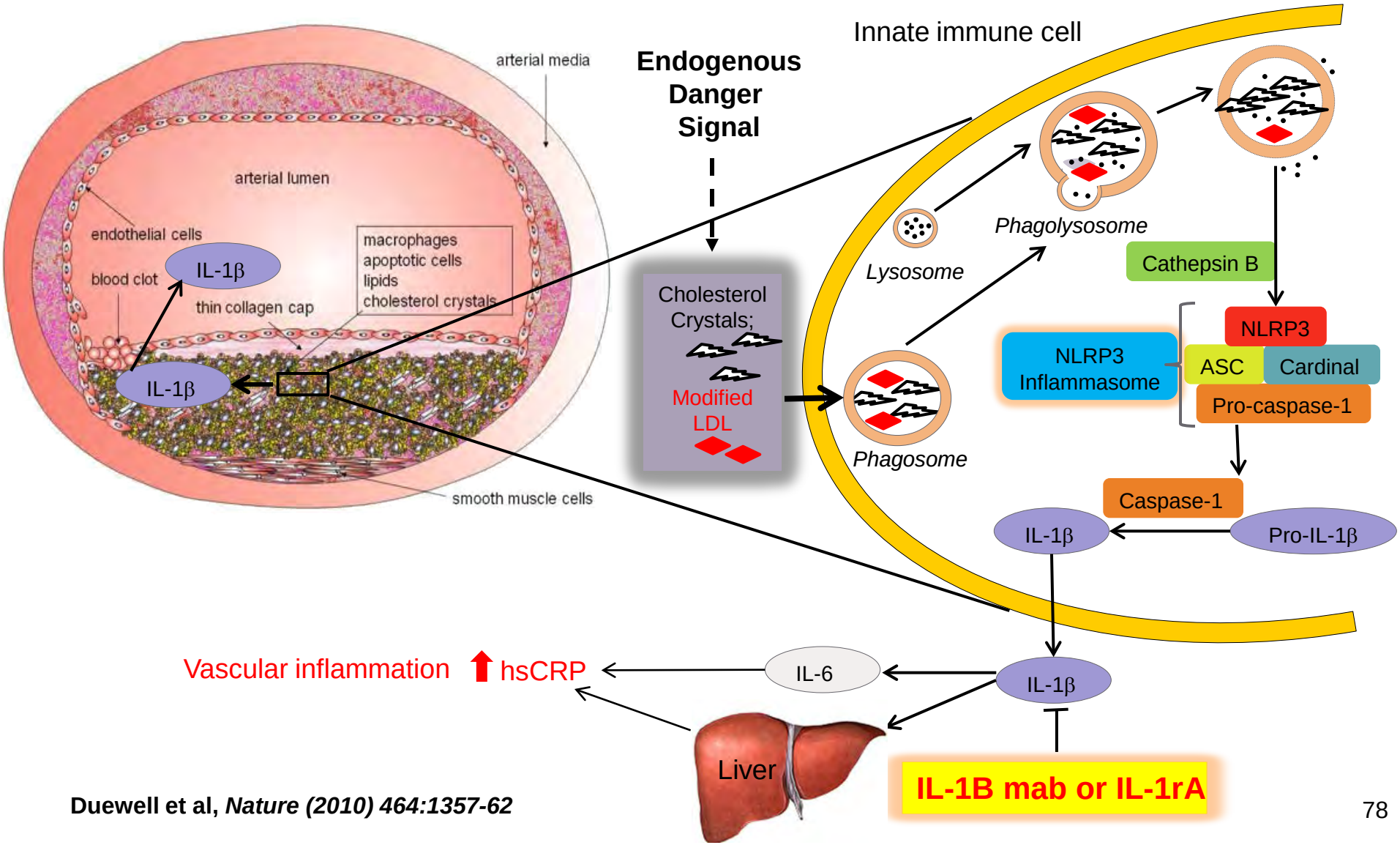
PLoS one

Cholesterol Crystals Activate the NLRP3 Inflammasome in Human Macrophages: A Novel Link between Cholesterol Metabolism and Inflammation

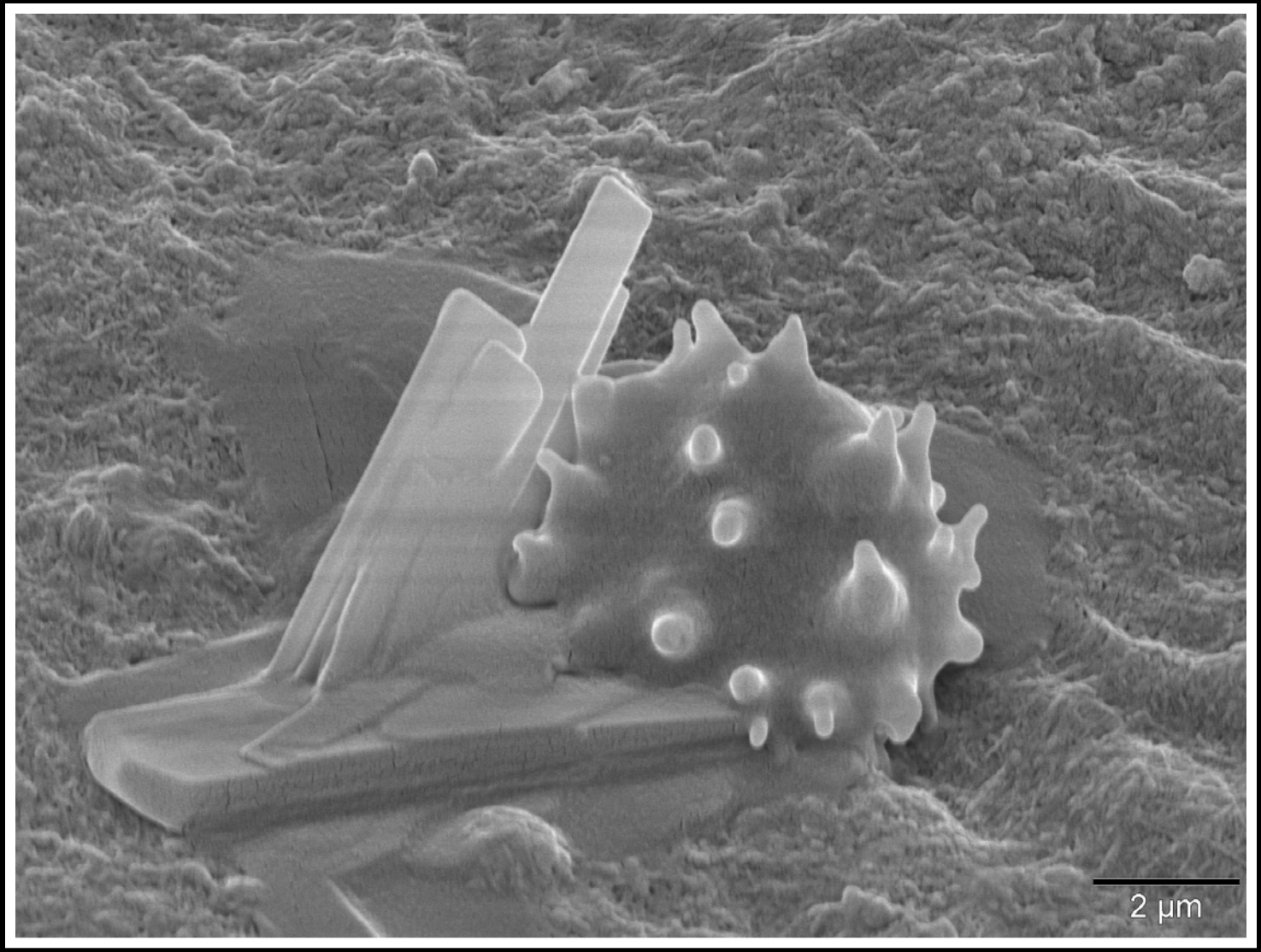
Kristiina Rajamäki[1]*, Jani Lappalainen[1], Katariina Öörni[1], Elina Välimäki[2], Sampsa Matikainen[2], Petri T. Kovanen[1], Kari K. Eklund[1]

1 Wihuri Research Institute, Helsinki, Finland, 2 Finnish Institute of Occupational Health, Helsinki, Finland

Cholesterol crystals activate the caspase-1-activating NLRP3 inflammasome to generate IL-1β and initiate atherosclerosis

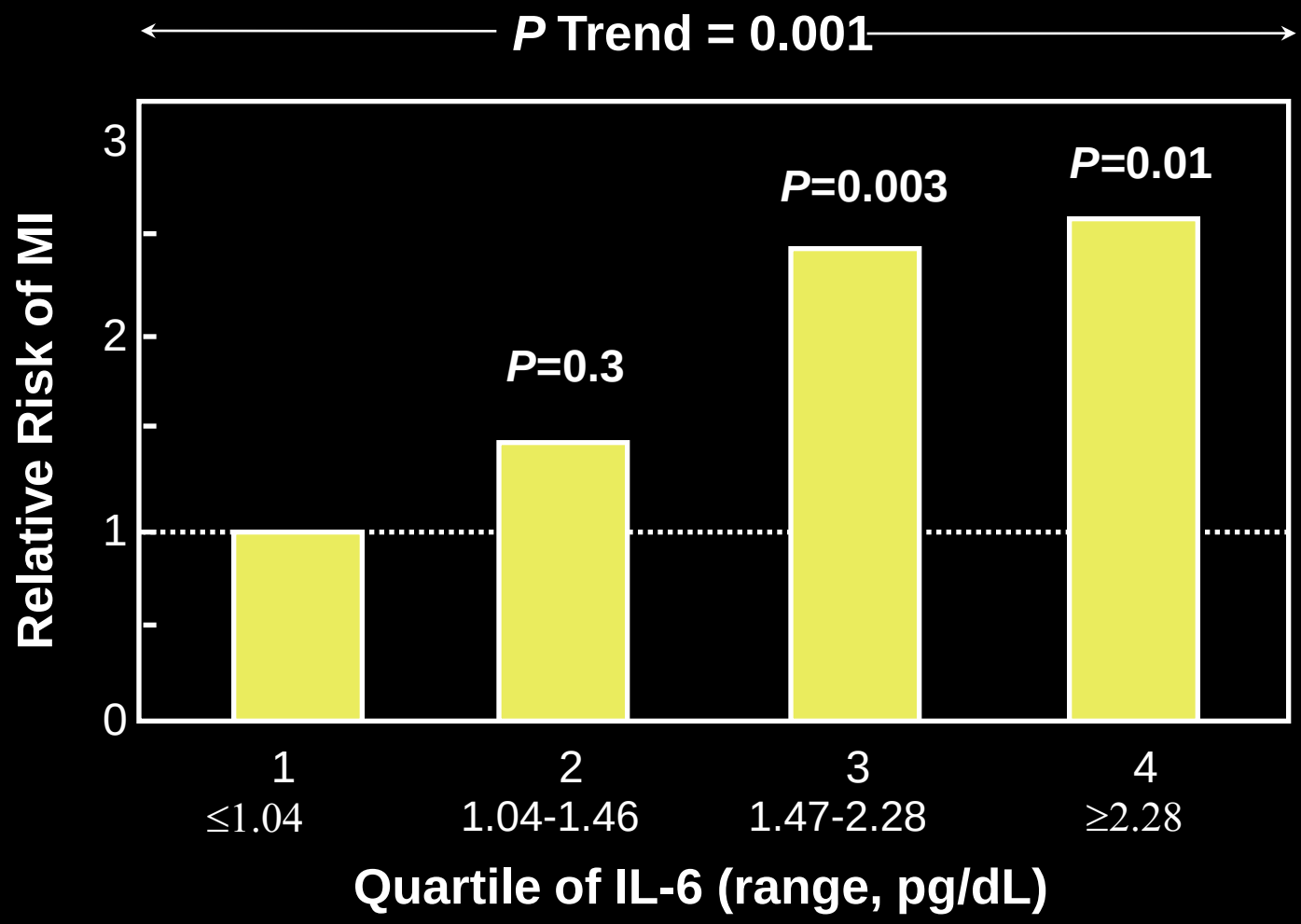


Duewell et al, *Nature (2010) 464:1357-62*



Courtesy, George S. Abela, MD.

IL-6 and Risk of Future MI in Apparently Healthy Men



Ridker et al, Circulation 2000;101:1767-1772

Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

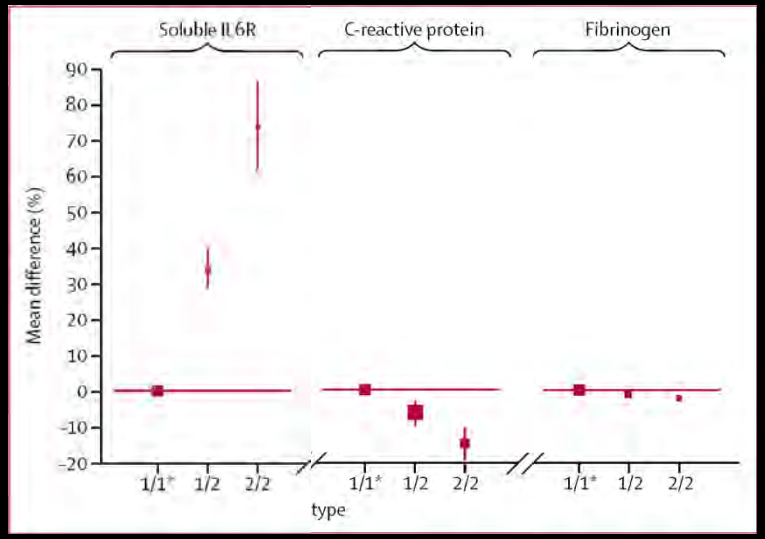
*IL6R Genetics Consortium and Emerging Risk Factors Collaboration**

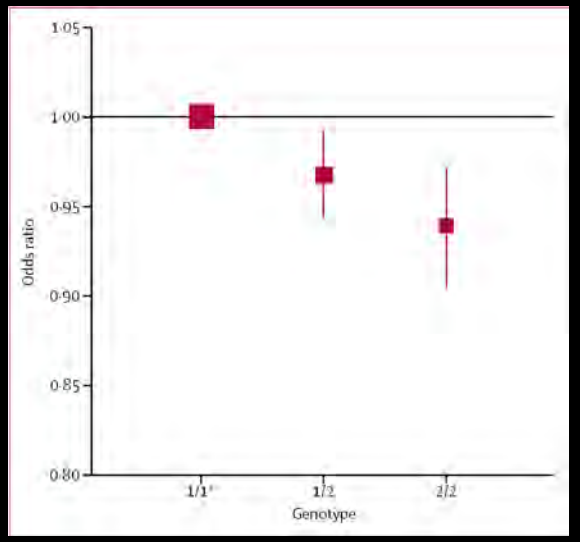
Summary

Background Persistent inflammation has been proposed to contribute to various stages in the pathogenesis of cardiovascular disease. Interleukin-6 receptor (IL6R) signalling propagates downstream inflammation cascades. To assess whether this pathway is causally relevant to coronary heart disease, we studied a functional genetic variant known to affect IL6R signalling.

Published Online March 14, 2012 DOI:10.1016/S0140-6736(11)61931-4

See Online/Comment





IL6R Consortium and Emerging Risk Factors Collaboration, The Lancet 2012

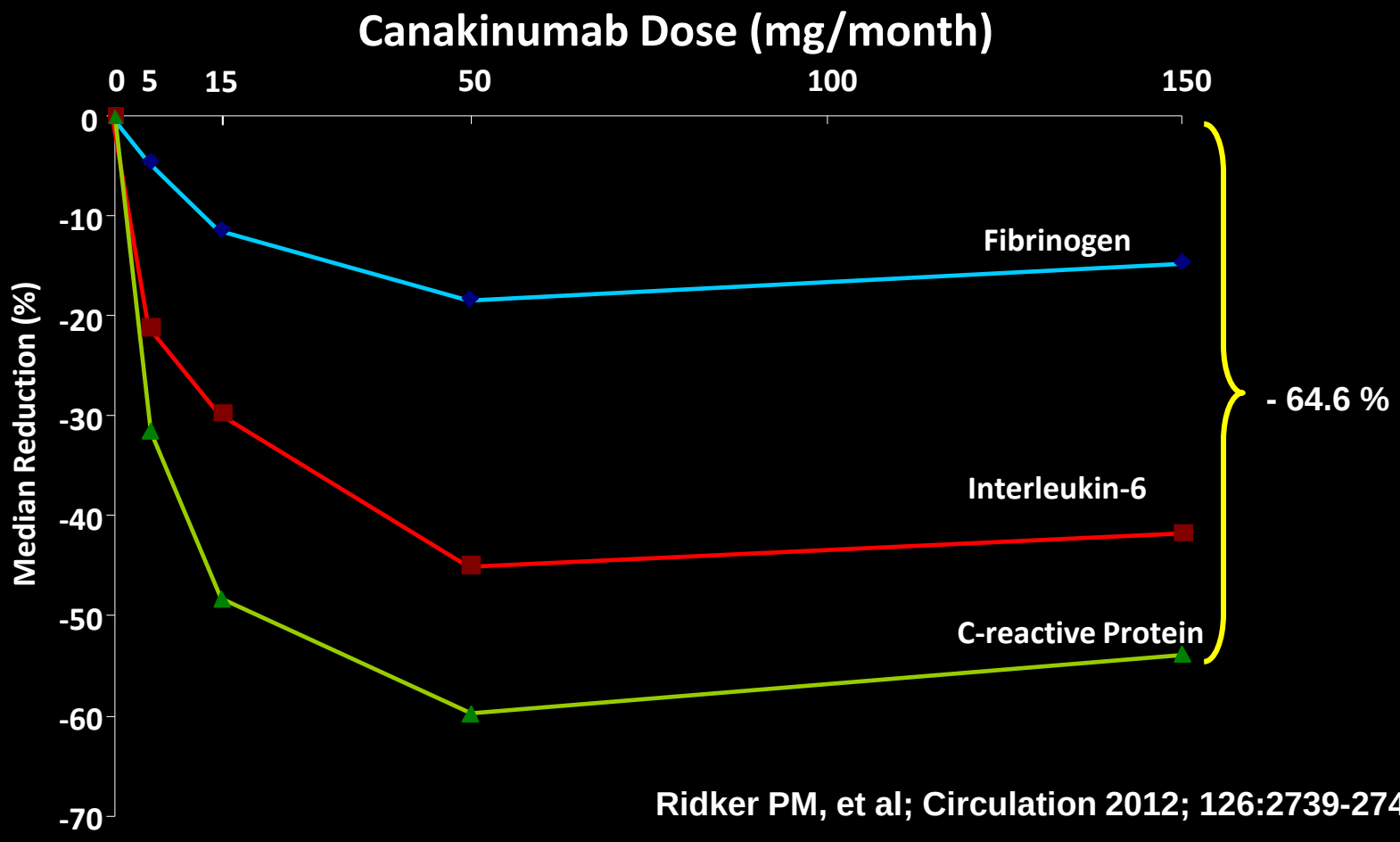
Canakinumab (Ilaris, Novartis)

- **high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)**
- **designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine**
- **long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months**

Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial

Paul M Ridker, MD, MPH; Campbell P. Howard, MD; Verena Walter, Dipl Math (FH); Brendan Everett, MD; Peter Libby, MD; Johannes Hensen, MD; Tom Thuren, MD, PhD, on behalf of the CANTOS Pilot Investigative Group



Ridker PM, et al; Circulation 2012; 126:2739-2748

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) (Ridker PI)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (≥ 2 mg/L)

N = 17,200
Novartis
(>6000 currently)

Randomized
Canakinumab 50 mg
SC q 3 months

Randomized
Canakinumab 150 mg
SC q 3 months

Randomized
Canakinumab 300 mg
SC q 3 months

Randomized
Placebo
SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CHF; PCI/CABG; biomarkers

THE WALL STREET JOURNAL.

MONDAY, SEPTEMBER 3, 2012

Trying a New Line of Attack in Heart Disease

Two Major Clinical Trials Test If Treating Inflammation Can Cut the Risk of a Heart Attack or Stroke

By Ron Winslow

Two major clinical trials are testing for the first time whether treating inflammation can reduce the risk of a heart attack or stroke, potentially opening up a new line of attack in the battle against cardiovascular disease.

Until now, strategies to fight these killers have focused largely on well-known risk factors such as high blood process with anti-inflammatory drugs isn't known.

"This goes beyond simply asking, is inflammation a marker of risk (for cardiovascular disease) to asking if it's a target for therapy," said Paul M. Ridker, director of the center for cardiovascular-disease prevention at Harvard-affiliated Brigham and Women's Hospital in Boston, who is leading both trials.

These are especially high-risk patients for whom current optimal treatment often fails. "We've kind of run out of our tool kit for these individuals and yet they're still having events," said Gary Gibbons, director of the NIH's National Heart, Lung and Blood Institute, which officially funded the study.

The Novartis trial, which is testing the company's anti-inflammatory

THE WALL STREET JOURNAL.

MONDAY, SEP

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NEWS&ANALYSIS

Science 2012

CARDIOVASCULAR DISEASE

Massive Trials to Test Inflammation Hypothesis

It's not often that eminent scientists enlist 24,000 volunteers and tens of millions of dollars to put their credibility on the line, but that's exactly what cardiologist Paul Ridker is doing. More than 20 years ago, early in his career at Harvard Medical School's Brigham and Women's Hospital in Boston, he began nurturing the idea that inflammation is deeply intertwined with cardiovascular disease. Ridker has never been able to prove that the body's inflammatory response causes heart attacks—or that blocking it can save lives. But he has built his case bit by bit. Now, his theory is being put to the test in a pair of massive clinical trials, both of which he's heading. One was launched last year by Novartis, and the other was announced last month by the U.S. National Heart, Lung, and Blood Institute (NHLBI).

"This is testing a whole new paradigm, a whole new approach, towards treating atherosclerosis," because anti-inflammatory drugs are not now a therapy of choice, says Michael Lauer, director of the Division of Cardiovascular Sciences at NHLBI. Ridker's trial went through five rounds of review before being approved.

Ridker is well known among cardiologists to treat rheumatoid arthritis and, at much higher doses, certain cancers. The Novartis trial is recruiting 17,000 others, about three-quarters of whom will inject different doses of a monoclonal antibody approved for an extremely rare class of inflammatory diseases. Both trials will treat patients for up to 4 years. Novartis has not revealed the cost of its trial, but NHLBI is budgeting nearly $80 million.

"Half the world said Paul is wrong, and the other half said Paul is right," says John Kastelein, a vascular medicine specialist at the Academic Medical Center in Amsterdam. Ridker has some recent findings on his side. Among them is a paper published in *The Lancet* in March by a worldwide genetics consortium. The group found that people with a gene variant that blunted interleukin-6 signaling, and thereby reduced sys-

benefits of the drugs came from targeting inflammation, or from their anticlotting or anticholesterol effects. But he couldn't get a definitive answer. Crestor may have helped not because it lowered CRP but because it pushed cholesterol down in people with supposedly normal levels. The results were only "indirect suggestions" about inflammation's role, Ridker admits.


THE WALL STREET JOURNAL.

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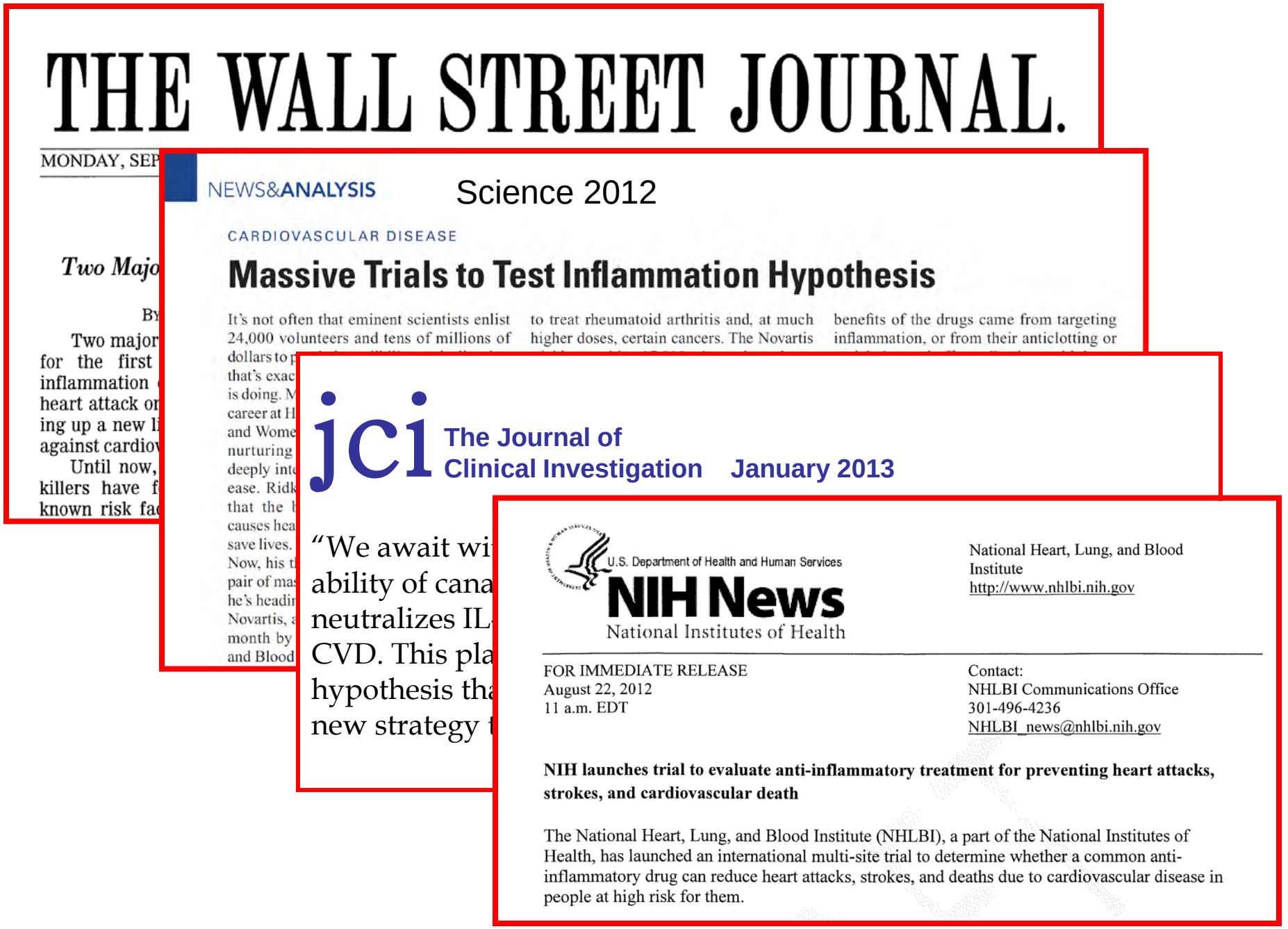
Science 2012

jci The Journal of Clinical Investigation January 2013

"We await with great interest the outcome of an ongoing trial of the ability of canakinumab, a human monoclonal antibody that neutralizes IL-1β, to reduce CVD in high-risk patients with existing CVD. This placebo controlled study will be a key test of the hypothesis that inhibition of inflammation will be an important new strategy to reduce the burden of CVD"



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NEWS&ANALYSIS

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U.S. Department of Health and Human Services
NIH News
National Institutes of Health

National Heart, Lung, and Blood Institute
http://www.nhlbi.nih.gov

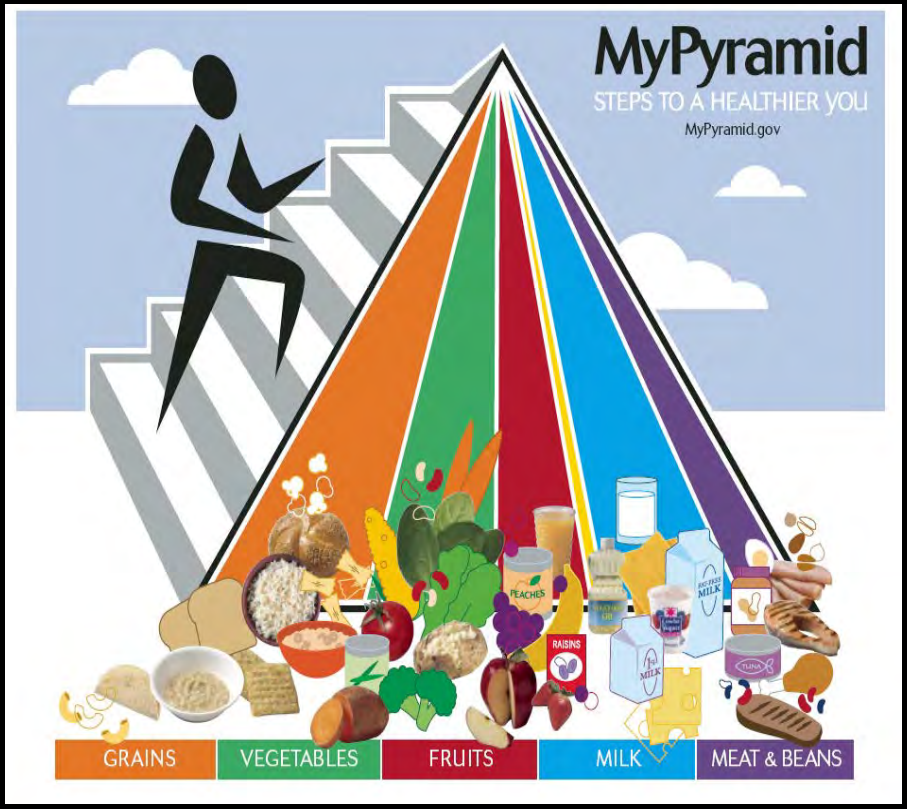
FOR IMMEDIATE RELEASE
August 22, 2012
11 a.m. EDT

Contact:
NHLBI Communications Office
301-496-4236
NHLBI_news@nhlbi.nih.gov

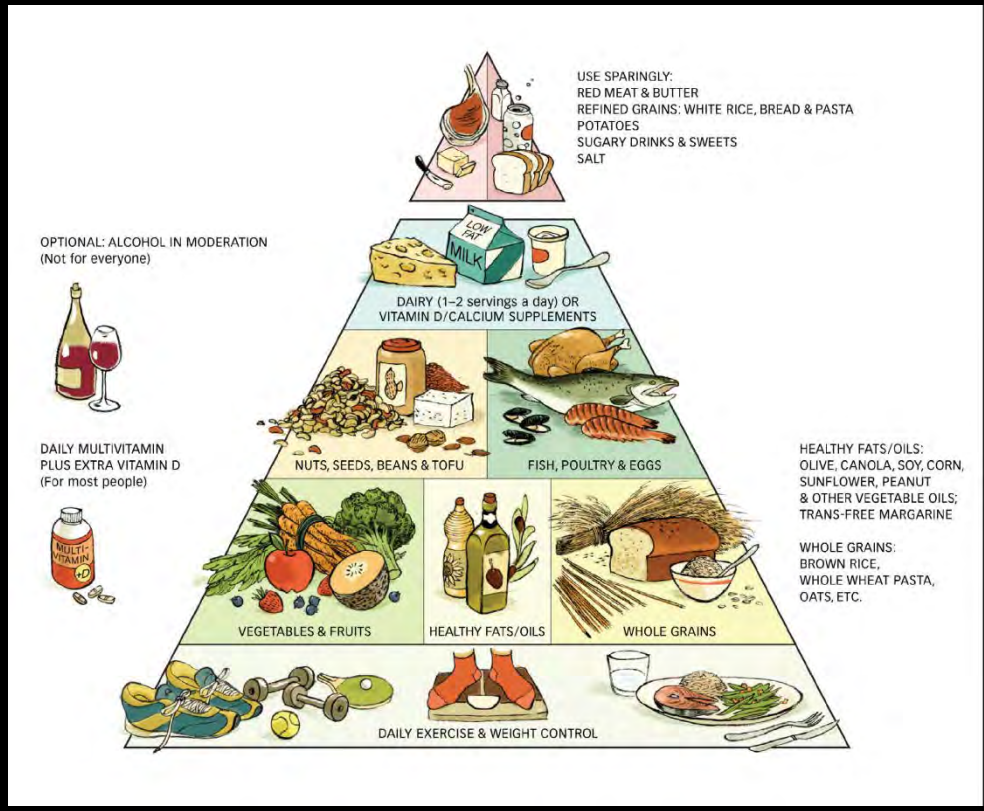
NIH launches trial to evaluate anti-inflammatory treatment for preventing heart attacks, strokes, and cardiovascular death

The National Heart, Lung, and Blood Institute (NHLBI), a part of the National Institutes of Health, has launched an international multi-site trial to determine whether a common anti-inflammatory drug can reduce heart attacks, strokes, and deaths due to cardiovascular disease in people at high risk for them.

Probiotics, Inflammation, Weight Loss, and Vascular Risk



FDA Food Pyramid



HSPH Food Pyramid

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Primary Prevention of Cardiovascular Disease with a Mediterranean Diet

Ramón Estruch, M.D., Ph.D., Emilio Ros, M.D., Ph.D., Jordi Salas-Salvadó, M.D., Ph.D., Maria-Isabel Covas, D.Pharm., Ph.D., Dolores Corella, D.Pharm., Ph.D., Fernando Arós, M.D., Ph.D., Enrique Gómez-Gracia, M.D., Ph.D., Valentina Ruiz-Gutiérrez, Ph.D., Miquel Fiol, M.D., Ph.D., José Lapetra, M.D., Ph.D., Rosa Maria Lamuela-Raventos, D.Pharm., Ph.D., Lluís Serra-Majem, M.D., Ph.D., Xavier Pintó, M.D., Ph.D., Josep Basora, M.D., Ph.D., Miguel Angel Muñoz, M.D., Ph.D., José V. Sorlí, M.D., Ph.D., José Alfredo Martínez, D.Pharm, M.D., Ph.D., and Miguel Angel Martínez-González, M.D., Ph.D., for the PREDIMED Study Investigators*

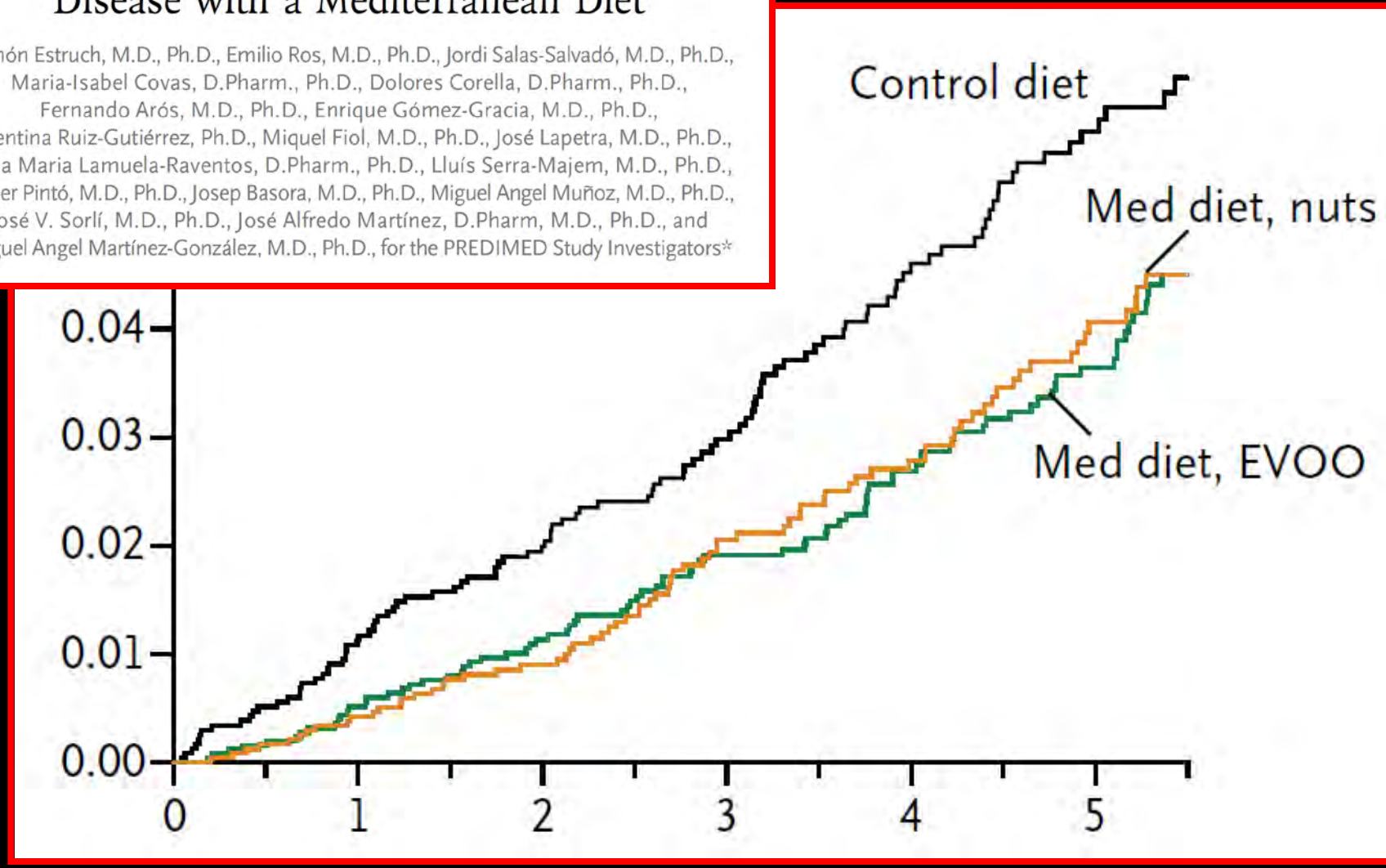
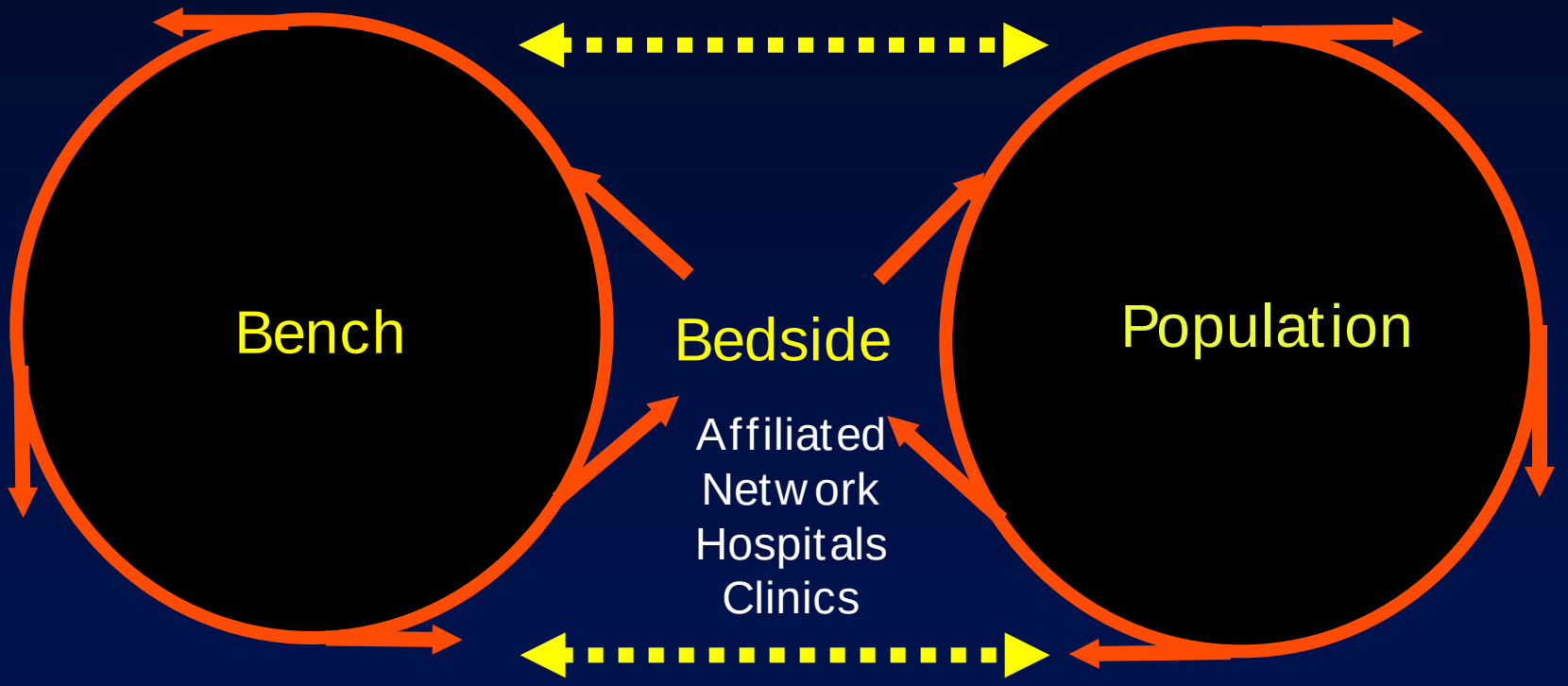


Photo courtesy of Randal Thomas

Advertisement Campaigns

- $635 million (McDonald's)
- $298 million (Burger King)
- $224 million (Coca Cola)

What is translational research? How does an integrated health care system support it?



T1, T2, T3

SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS*

By WILLIAM S. TILLETT, M.D., and THOMAS FRANCIS, Jr., M.D.

(*From the Hospital of The Rockefeller Institute for Medical Research*)

(Received for publication, June 26, 1930)

It has been shown (1) that pneumococci contain two constituents which are chemically and antigenically distinct. One of these, the type-specific component, is a complex polysaccharide, predominantly present in the capsule of the organism; the other, a substance common to the pneumococcus species, is the so-called nucleoprotein, contained for the most part in the body of the cell. That these two chemically distinct fractions are responsible for the production of two qualitatively different antibodies has been demonstrated (1, 2).

The present report is based upon observations made with a third fraction derived from pneumococci and chemically distinct from both type-specific capsular polysaccharide and non-type-specific somatic nucleoprotein. For purposes of reference this substance is designated Fraction C. The chemical nature of Fraction C and the method of purification together with certain experimental observations are presented in a separate communication (3). In this report it is sufficient to state that Fraction C is a non-protein material of somatic origin and appears to be a carbohydrate common to the pneumococcus species. Although final proof of its exact nature rests upon chemical analysis, nevertheless convincing evidence of the separate identity of Fraction C is brought out by the serological reactions to be described.

Material and Methods

Preparation of Fraction C.—The material employed in the serological tests was derived from a degraded, non-type-specific R strain of Pneumococcus. A strain of this character was employed in order to minimize the presence of type-specific carbohydrate. Fraction C was obtained in the following manner: The organisms

* Presented before the American Society for Clinical Investigation at a meeting held in Atlantic City, May 5, 1930.

Tillett and Francis
J Exp Med 1930

3rd serologic fraction
"fraction C"
isolated
from patients
infected with
pneumococcus
"C-reactive protein"

FIG. 1. Crystals of C-protein. × 100.

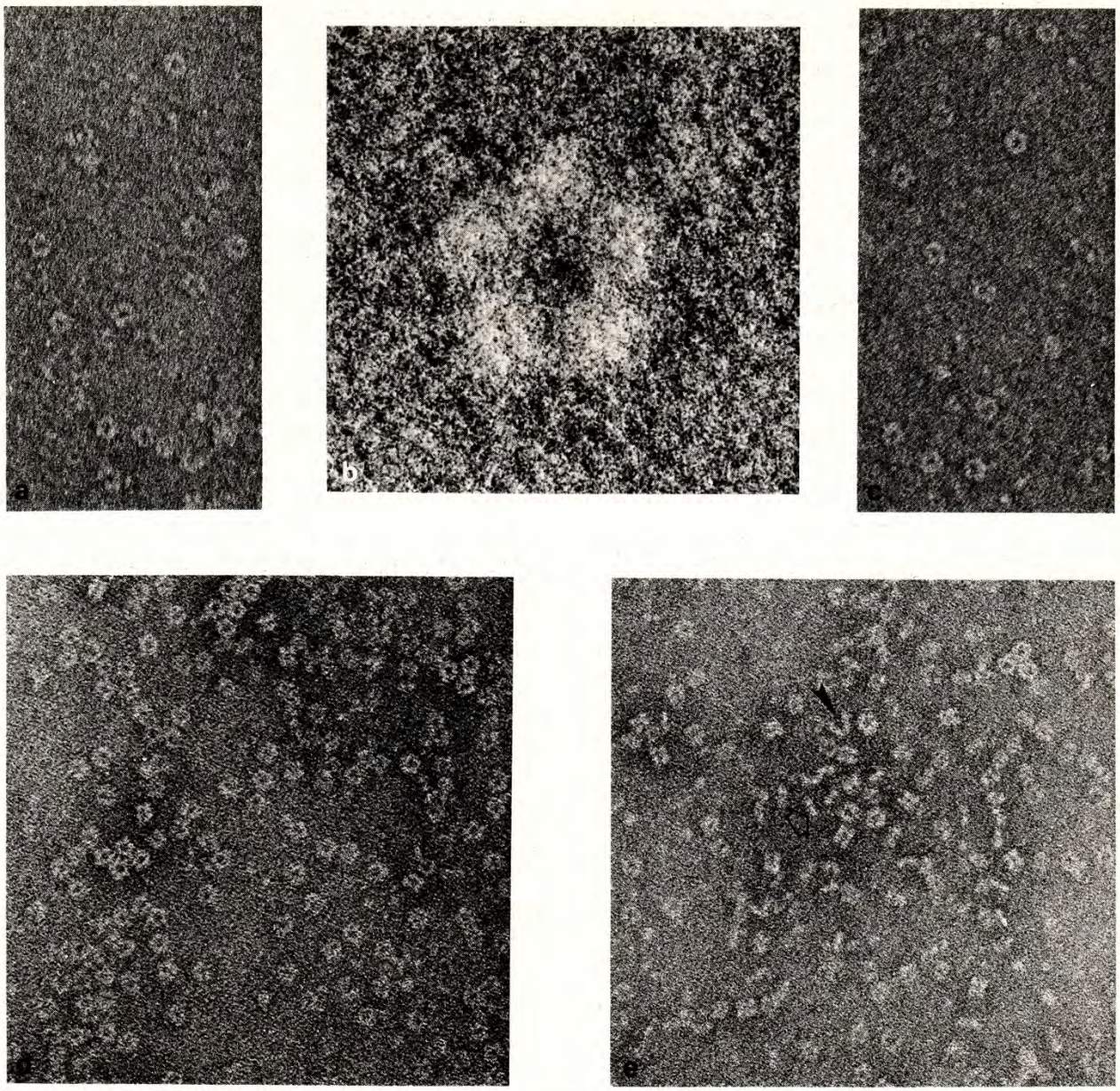
suspended in 35 cc. of physiological saline and brought into solution by the dropwise addition of saturated sodium citrate. A small amount of insoluble material was removed by centrifugation and discarded.

Crystallization.—The citrated solution (36 cc.) was mixed with an equal volume of saturated sodium sulfate solution (prepared at 37°C.) and held at 37°C. This step was included for its possible effect in causing further dissociation of the polysaccharide-protein complex by the action of the high salt concentration. The half-saturated solution remained entirely clear. After 2 hours an additional 72 cc. of saturated sodium sulfate was added, bringing the final concentration to 0.75 saturation. A light amorphous precipitate formed which

Maclyn McCarty
J Exp Med 1947;85:491-8

Crystallization of CRP

Maclyn McCarty
Oswald Avery, Colin MacLeod
“The Transforming Principle”
Genes are made of DNA



Osmond A Shelton E* PNAS 1977; 74:739-43

Pentraxin Structure

(NCI*)

Irving G. Kroop
June 2002

Proceedings of the Rudolf Virchow Medical Society
in the City of New York

BASEL (Switzerland) S. KARGER NEW YORK

Reprint *Vol. 14. 1955* Printed in Switzerland

C-REACTIVE PROTEIN IN CORONARY ARTERY DISEASE

IRVING G. KROOP*

A STUDY OF C-REACTIVE PROTEIN IN THE SERUM OF PATIENTS WITH CONGESTIVE HEART FAILURE

SAMUEL K. ELSTER, M.D.
EUGENE BRAUNWALD, M.D.
and
HARRISON F. WOOD, M.D.
New York, N. Y.

From the Departments of Medicine and Microbiology, The Mount Sinai Hospital, New York, Irvington House, Irvington-on-Hudson-New York, and the Department of Pediatrics, New York University College of Medicine

Reprinted from

AMERICAN HEART JOURNAL
St. Louis

Vol. 51, No. 4, Pages 533-541, April, 1956

(Printed in the U. S. A.)

To Paul -
Best wishes
Gene Braunwald

From the Departments of Medicine and Microbiology, The Mount Sinai Hospital, New York, Irvington House, Irvington-on-Hudson-New York, and the Department of Pediatrics, New York University College of Medicine.

Received for publication July 27, 1955.

*Rosenstock Foundation Fellow in Medicine.

**Postdoctoral Research Fellow of the National Heart Institute, U.S.P.H.S.

Inflammation, Atherothrombosis, and Vascular Prevention: Three Crucial Questions

Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? Yes

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? Yes

Is there evidence that reducing inflammation per se will reduce vascular events and slow progression of diabetes? CIRT, CANTOS – Lets find out

CARDIOVASCULAR INFLAMMATION REDUCTION TRIAL

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

For More Information : (855) 437-9330

theCIRT.org theCANTOS.org

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