Moving Novel Biomarkers (Genetic or Non-Genetic) From the Lab to the Clinic:

A Translational Cardiologist's Perspective (And A Cautionary Tale)

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Harvard Medical School
Director, Center for Cardiovascular Disease Prevention
Brigham and Women's Hospital, Boston MA

Dr. Ridker is listed as a co-inventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Seimens.

Prediction in Not Prevention

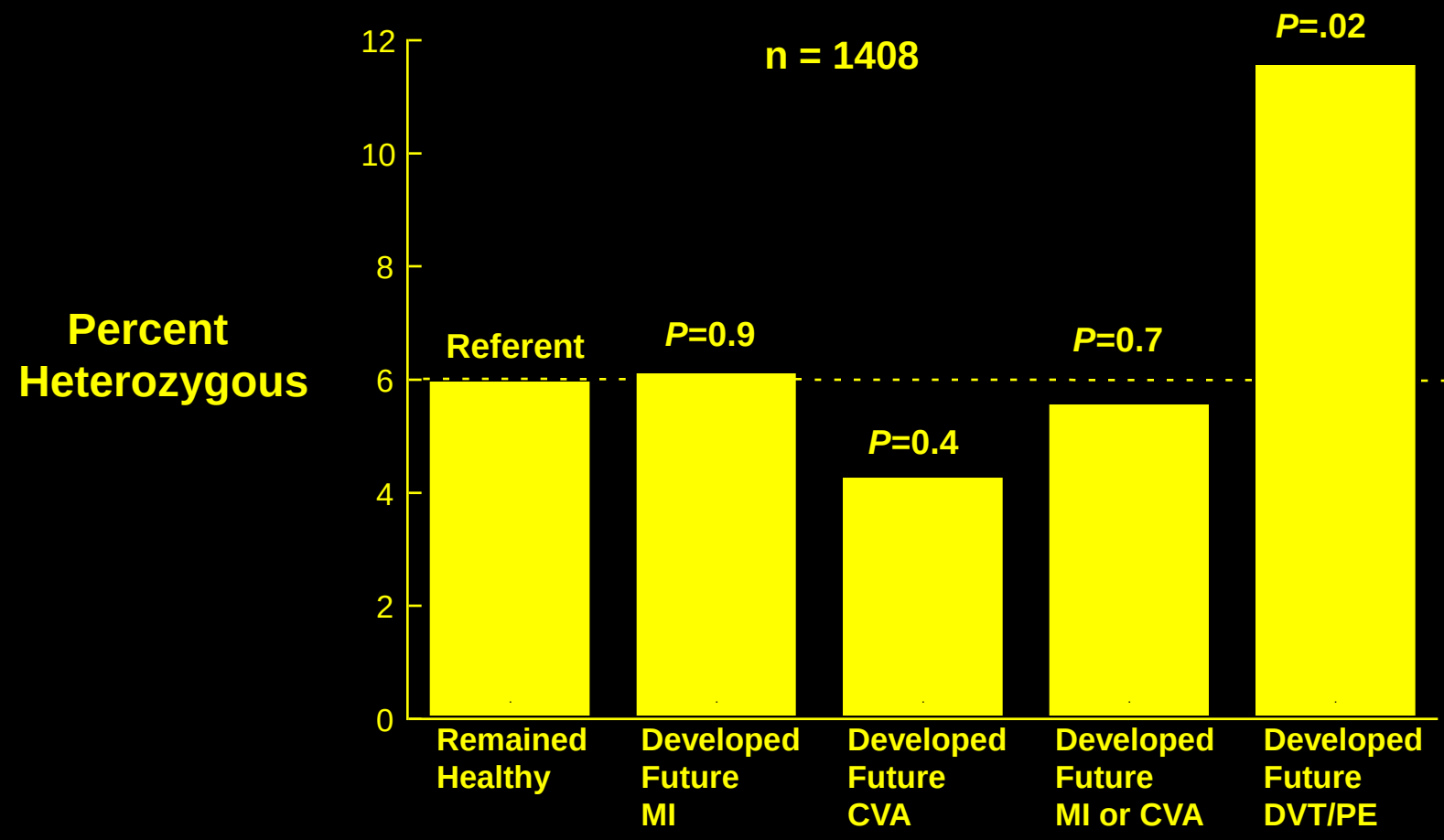
Many Clinicians Will Not Act Even After There is Hard Evidence That Knowing Something New Improves Care

Guidelines Usually Lag Clinical Data By Many Years and Rarely Are Evidence Based (Particularly Those that Claim to Be)

Physician Obstacles to Translation Are Large and Very Difficult To Surmount

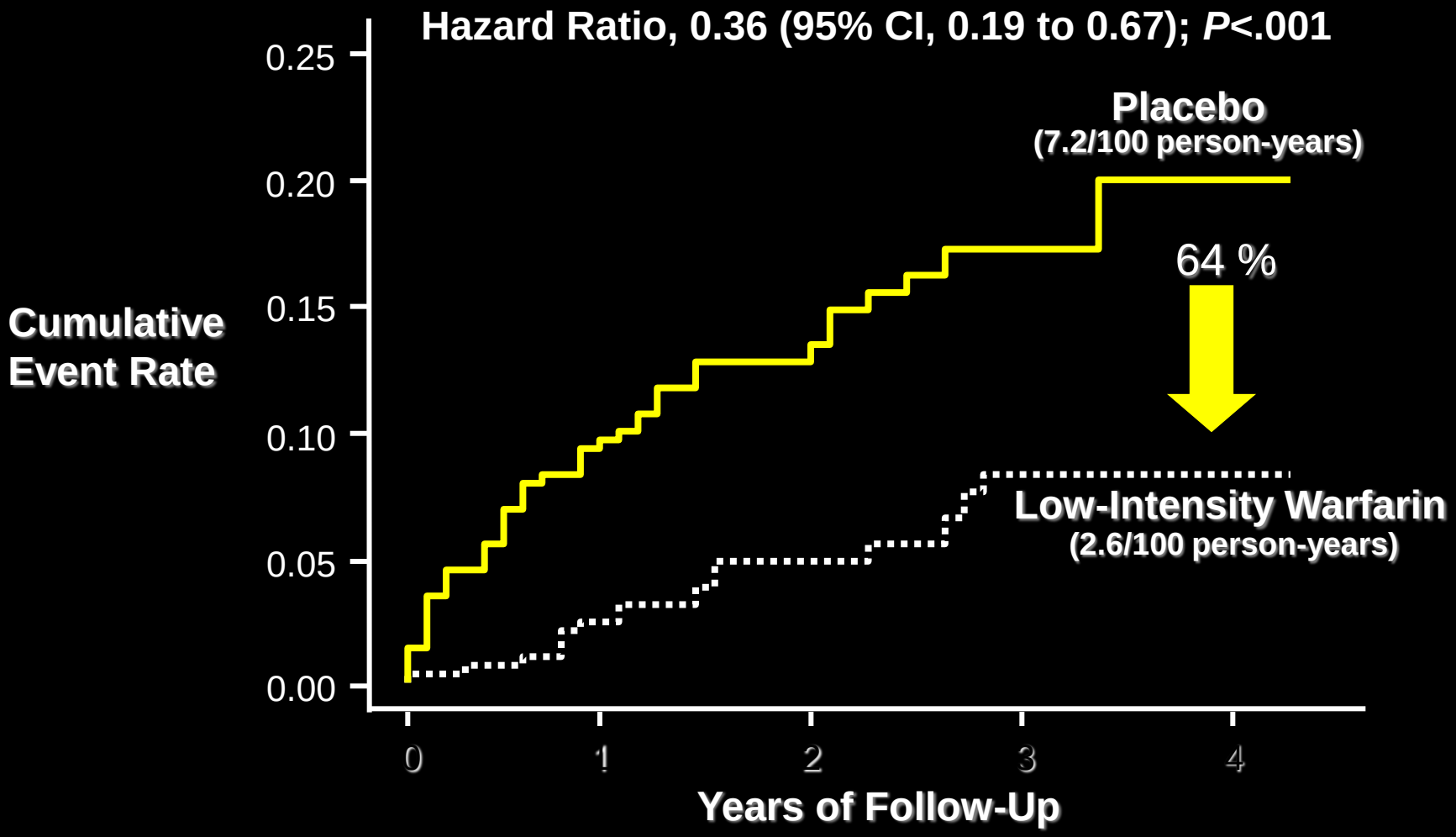
“All Change is For the Worse, Including Change For the Better”

G1691A Mutation in Coagulation Factor V and Risks of Future Arterial and Venous Thrombosis



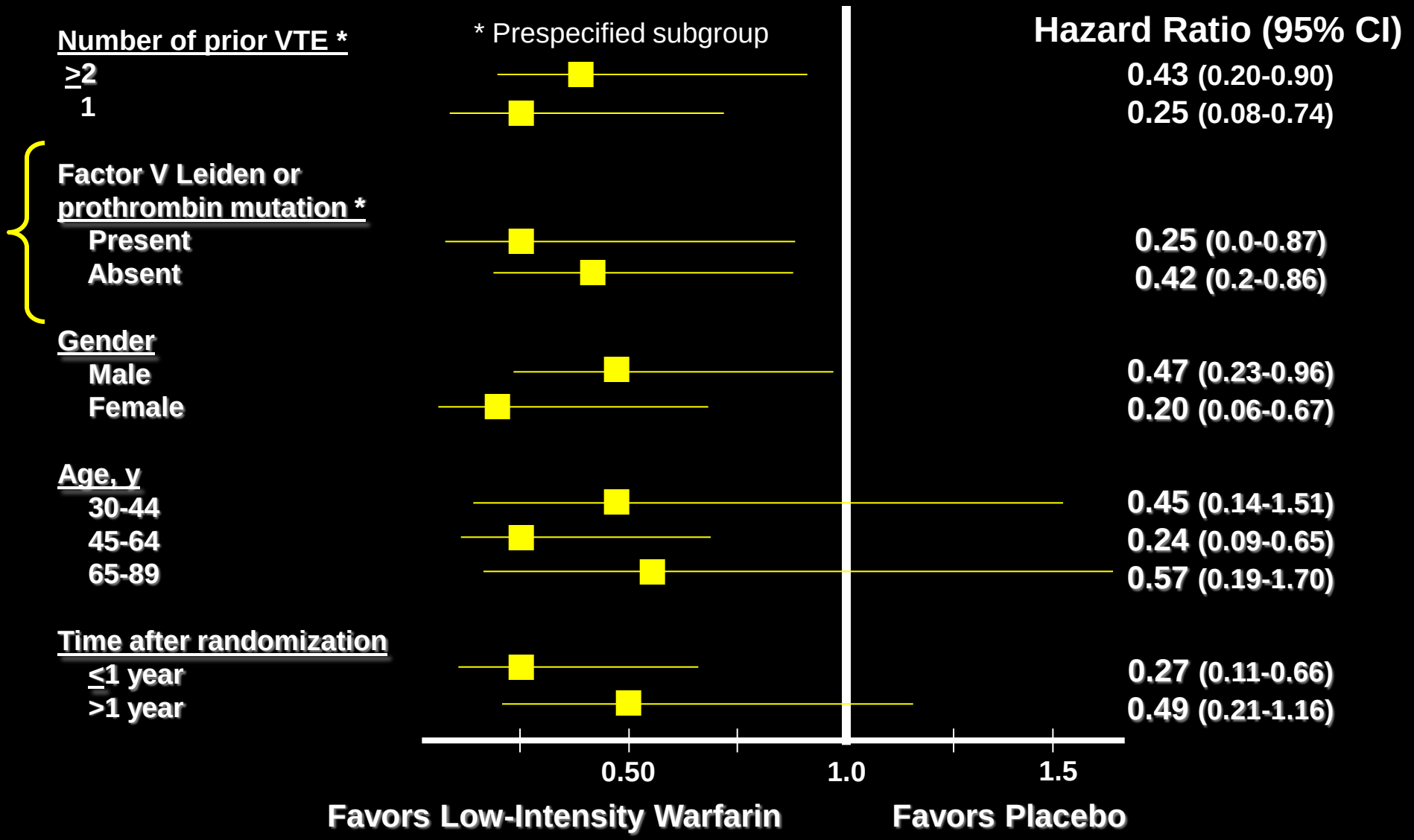
N Engl J Med. 1995;332:912-917.

PREVENT: NHLBI's First Pharmacogenetic Clinical Trial



N Engl J Med. 2003;348:1425-1434.

PREVENT: Recurrent VTE by Clinically Important Subgroups



N Engl J Med. 2003;348:1425-1434.

ORIGINAL CONTRIBUTION

Association Between a Literature-Based Genetic Risk Score and Cardiovascular Events in Women

Nina P. Paynter, PhD
Daniel I. Chasman, PhD
Guillaume Paré, MD, MS
Julie E. Buring, ScD
Nancy R. Cook, ScD
Joseph P. Miletich, MD, PhD
Paul M Ridker, MD, MPH

Context While multiple genetic markers associated with cardiovascular disease have been identified by genome-wide association studies, their aggregate effect on risk beyond traditional factors is uncertain, particularly among women.

Objective To test the predictive ability of a literature-based genetic risk score for cardiovascular disease.

Design, Setting, and Participants Prospective cohort of 19 313 initially healthy white women in the Women's Genome Health Study followed up over a median of 12.3 years (interquartile range, 11.6-12.8 years). Genetic risk scores were constructed from the National Human Genome Research Institute's catalog of genome-wide association study results published between 2005 and June 2009.

Main Outcome Measure Incident myocardial infarction, stroke, arterial revascularization, and cardiovascular death.

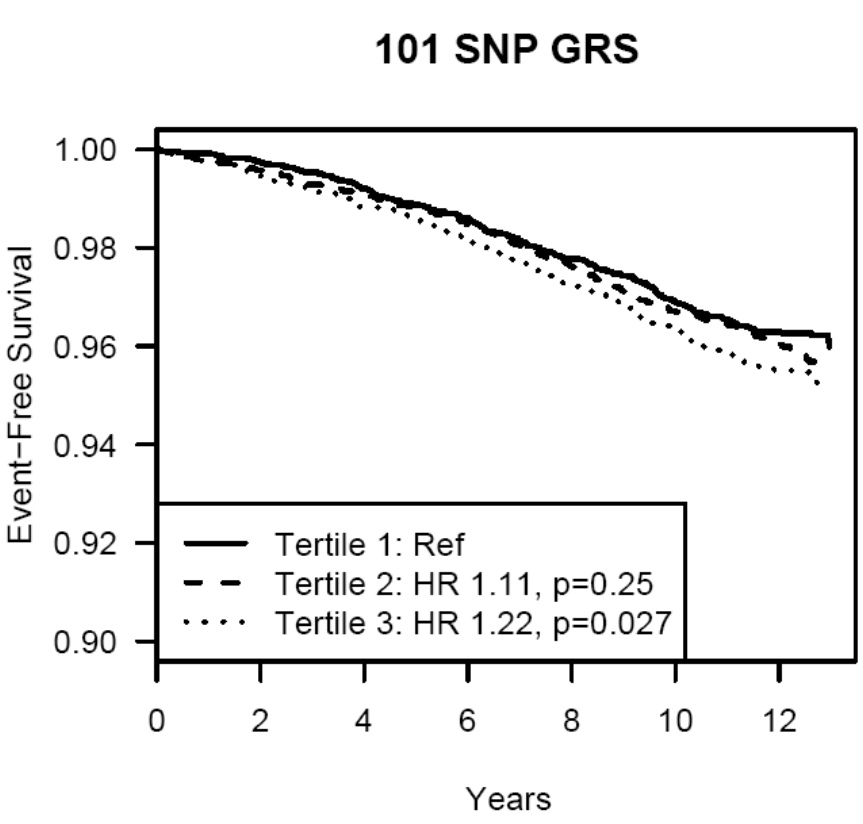
Results A total of 101 single nucleotide polymorphisms reported to be associated with cardiovascular disease or at least 1 intermediate cardiovascular disease phenotype at a published *P* value of less than 10^{-7} were identified and risk alleles were added to create a genetic risk score. During follow-up, 777 cardiovascular disease events occurred (199 myo-

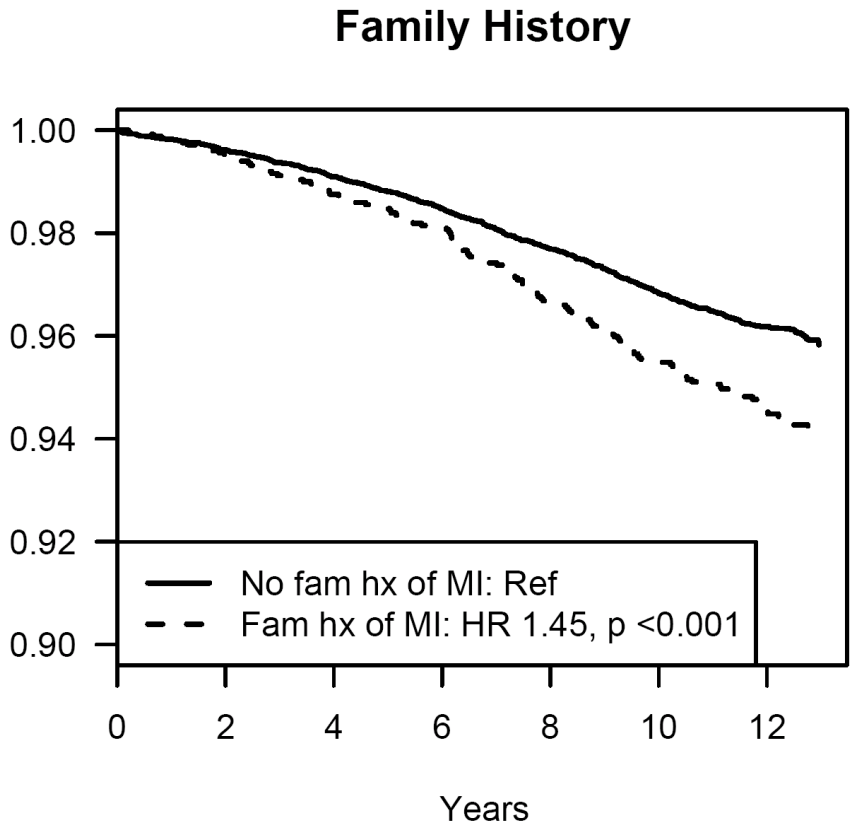
RISK PREDICTION IS A CENTRAL part of cardiovascular disease prevention and refining prediction strategies remains portant for targeting treatment recmendations. One area of potential provement has been the discovery of

JAMA 2010;303:631-637

Will Panels of Previously Validated SNPs Improve CVD Risk Prediction ?

WGHS: Women's Genome Health Study





JAMA 2010;303:631-637

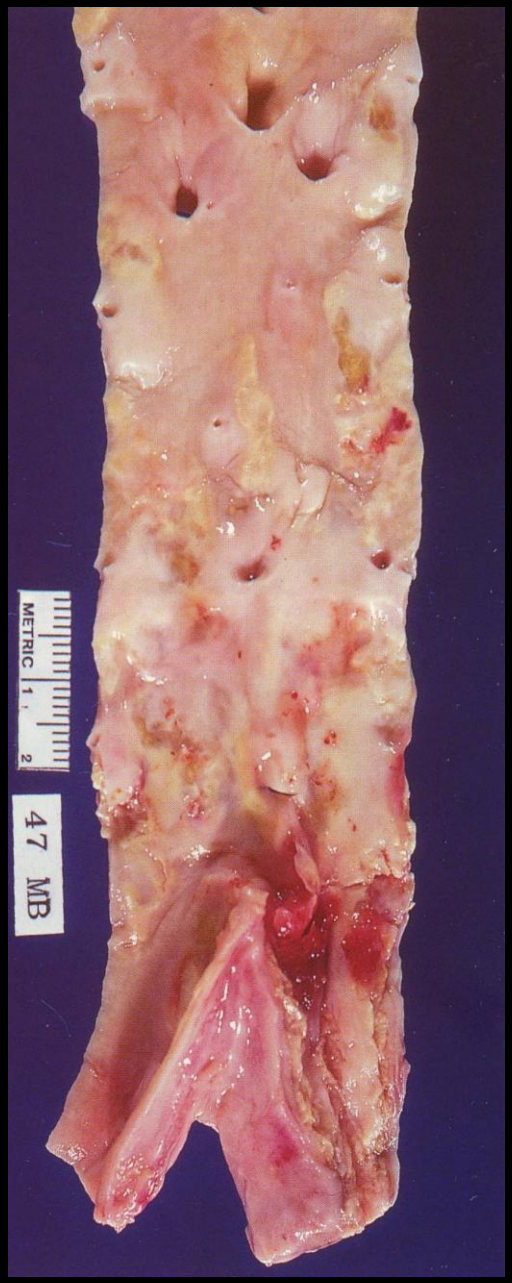
Moving A Biomarker From The Bench to the Clinic
Four Crucial Questions

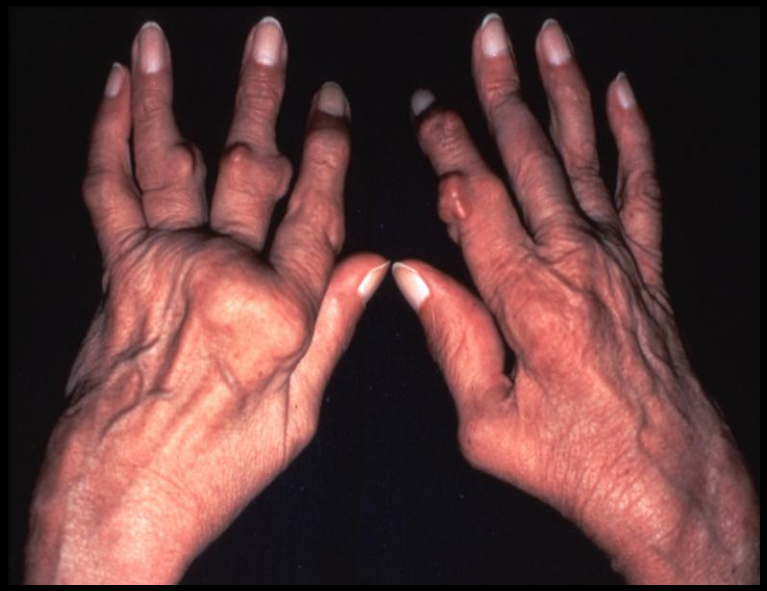
Is there evidence that individuals identified by the biomarker of interest are at high risk even when other risk factors are acceptable?

Is there evidence that individuals identified at increased risk due to the biomarker of interest benefit by receiving a therapy they otherwise would not have received?

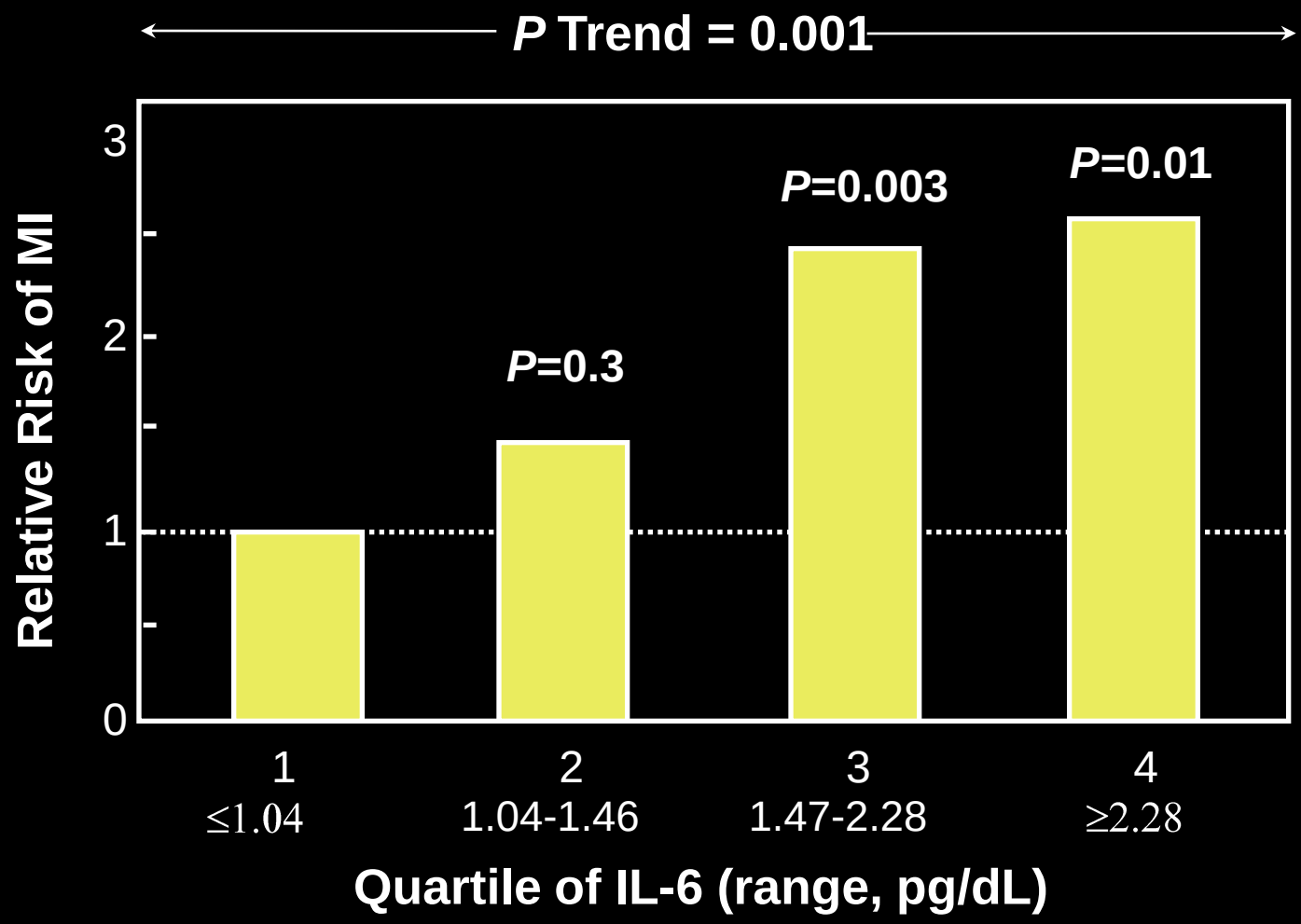
Is there evidence that individuals identified at increased risk due to the biomarker of interest benefit by avoiding a therapy they otherwise would have received?

Is there evidence that altering the biologic pathway reflected by the biomarker of interest reduces clinical event rates?


METRIC
47 MB



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



Circulation 2000;101:1767-1772

NATURE INSIGHT IN THIS ISSUE: THE EARLY UNIVERSE

27 April 2006 | www.nature.com/nature | $10

THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE

nature

RECORD RAINFALL FIGURES
Human fingerprints on the hydrological cycle

VIRTUAL ARCHAEOLOGY
Good science or good game?

BIRDSONG GRAMMAR
It's almost human

AIMING FOR THE HEART

C-reactive protein as a target for cardioprotective drugs

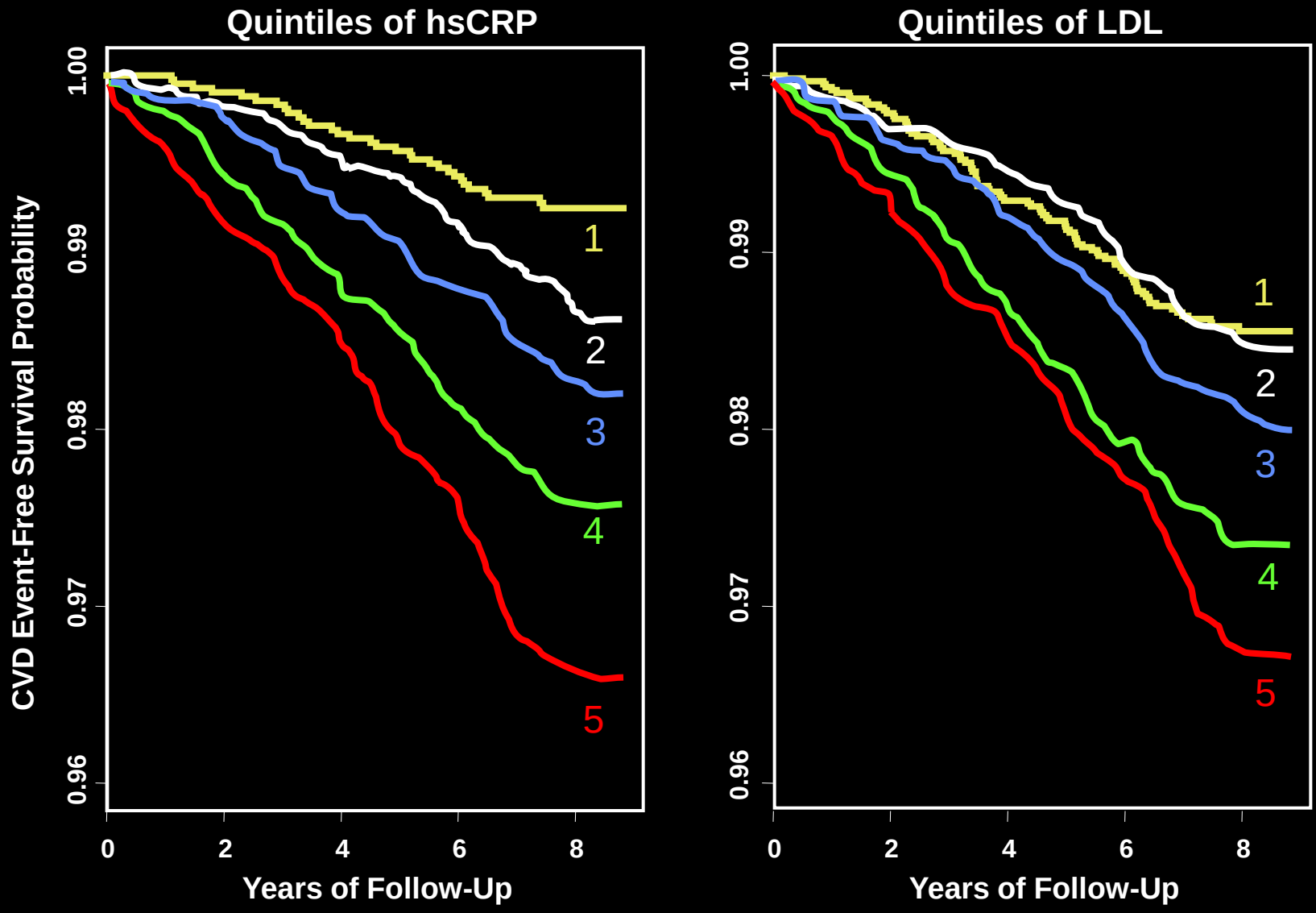
TECHNOLOGY FEATURE
Gene expression

$10.00US $12.99CAN

17

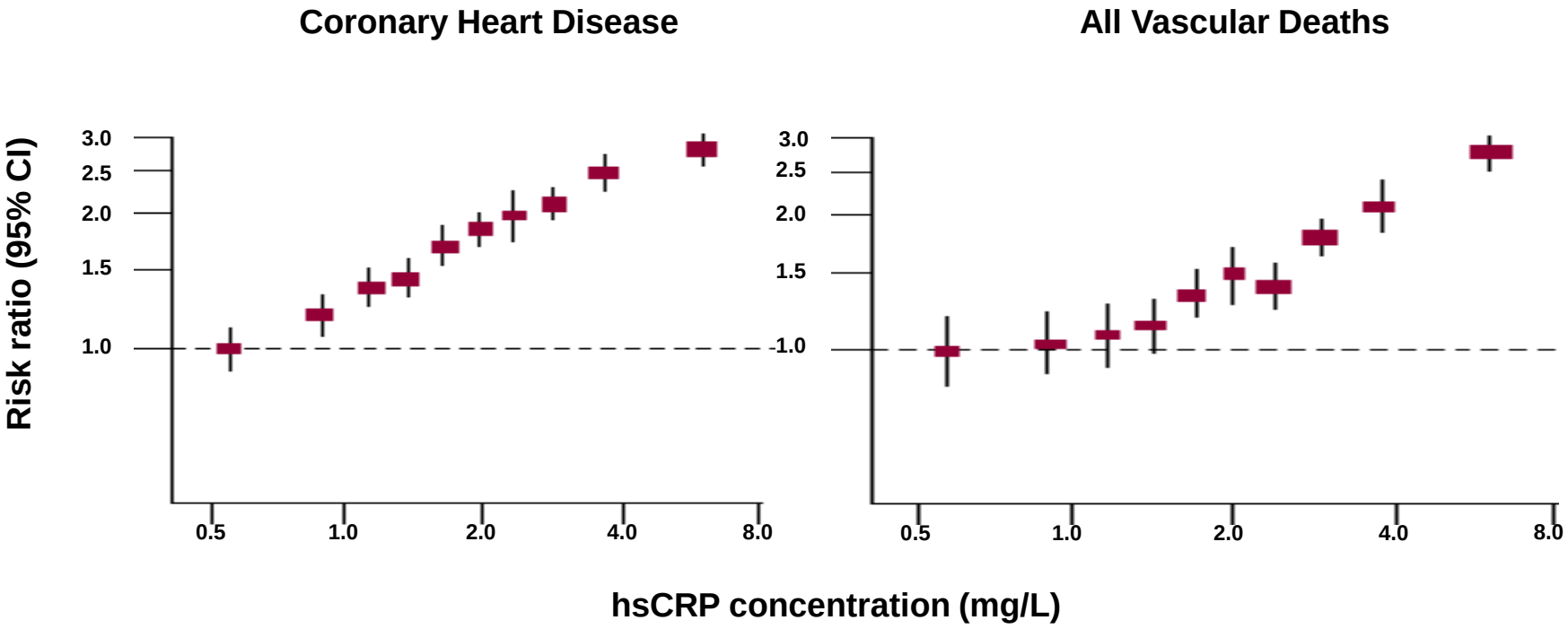
0 71486 03070 6

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



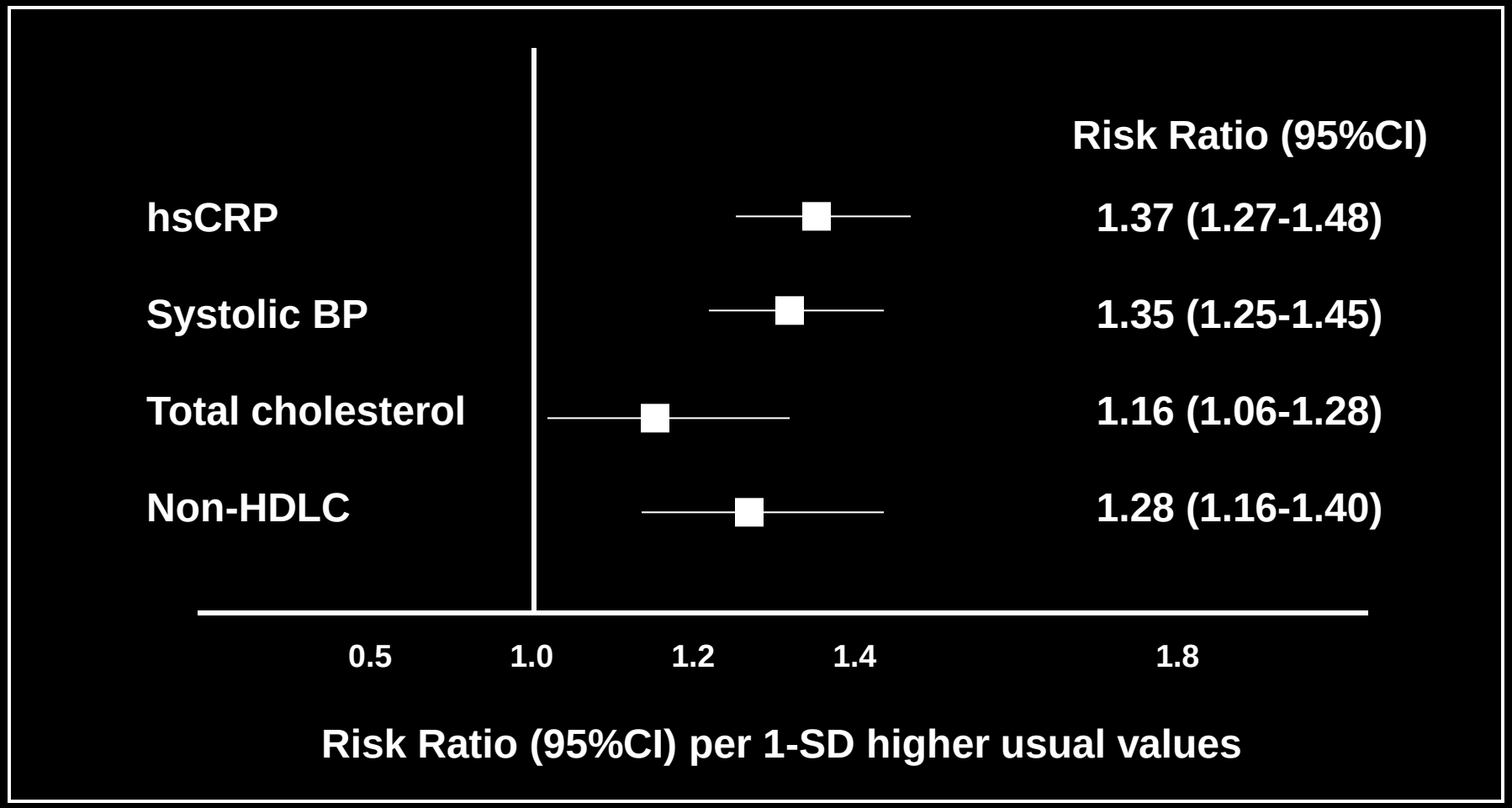
N Engl J Med. 2002;347:1157-1165.

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



Emerging Risk Factor Collaborators, Lancet January 2010

Meta-analysis of 54 Prospective Cohort Studies: The magnitude of independent risk associated with hsCRP 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

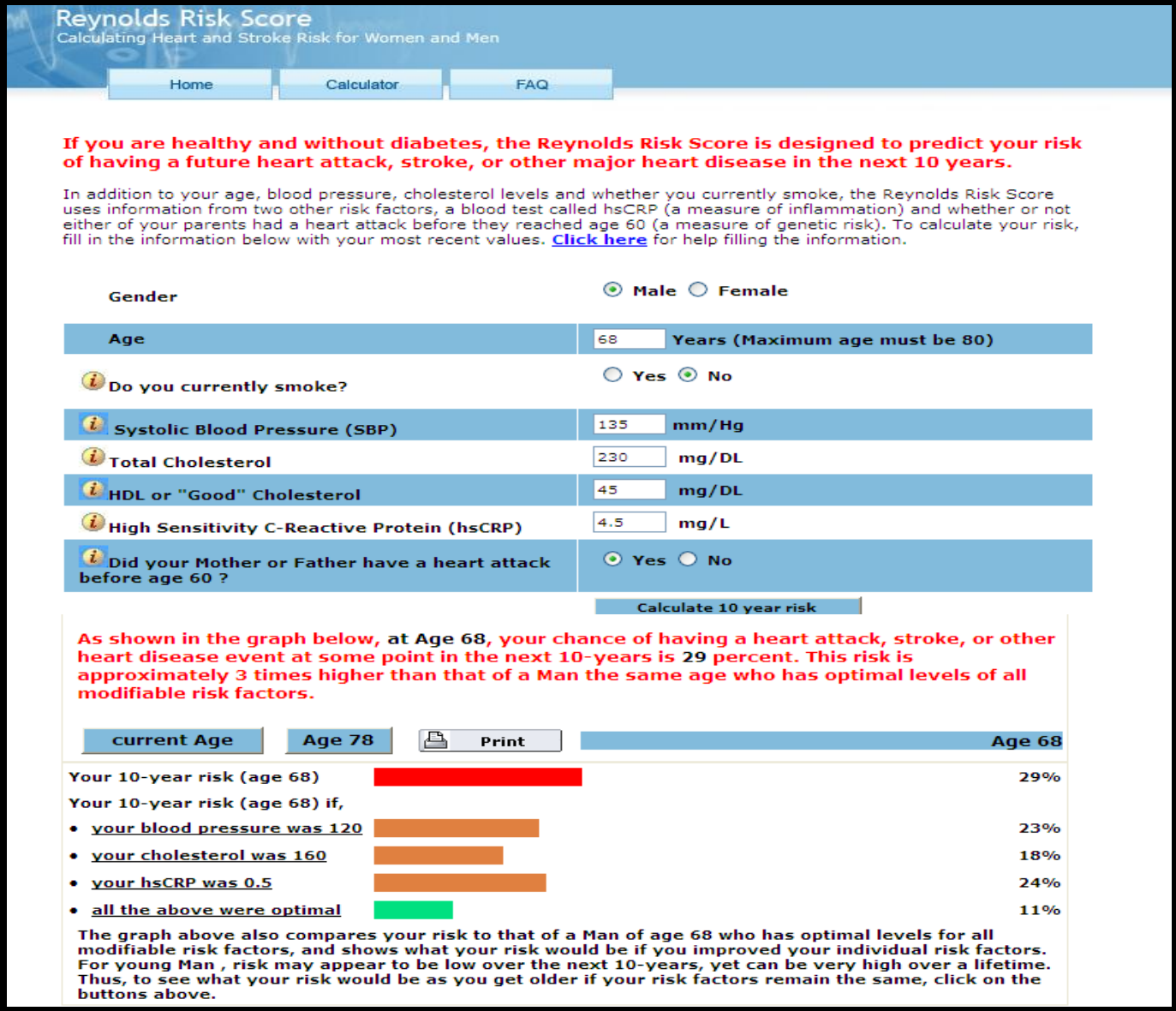
Emerging Risk Factor Collaborators, Lancet January 2010

www.reynoldsriskscore.org

Reynolds Risk Score

Age
Smoking
SBP
TC
HDLC
hsCRP
Family History

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



JAMA 2007;297:611-9

Circulation 2008;118:2243-51

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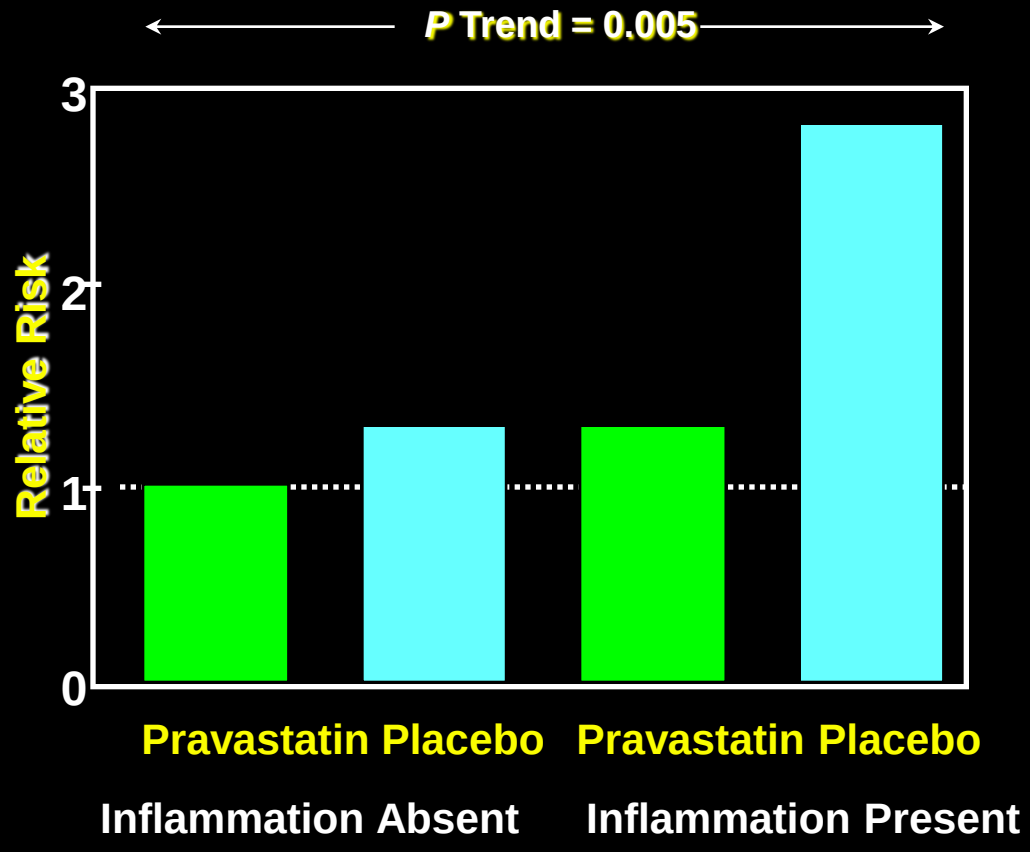
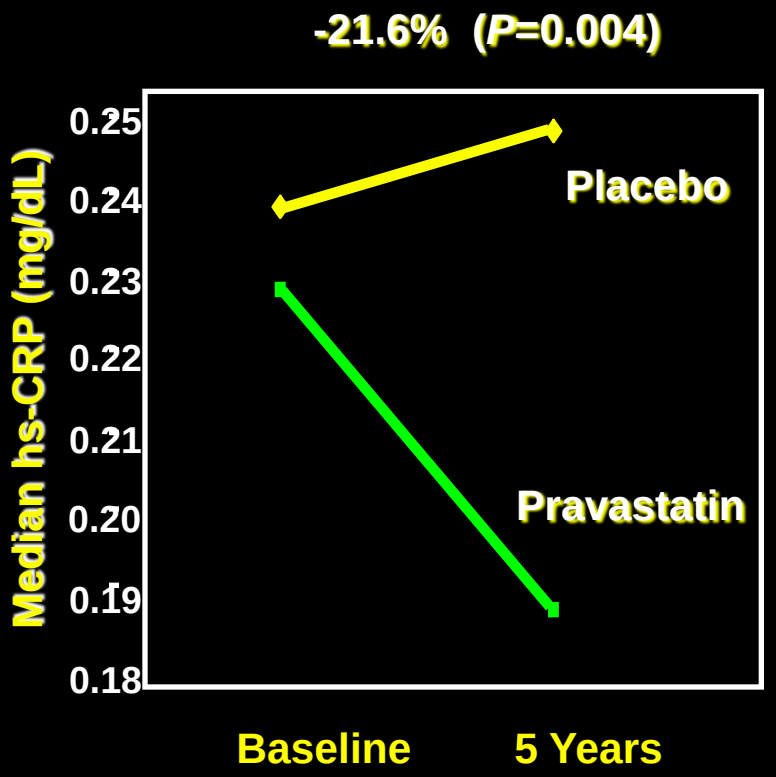
Inflammation, Statin Therapy, and hsCRP: Initial Observations



Circulation. 1998;98:839–844.



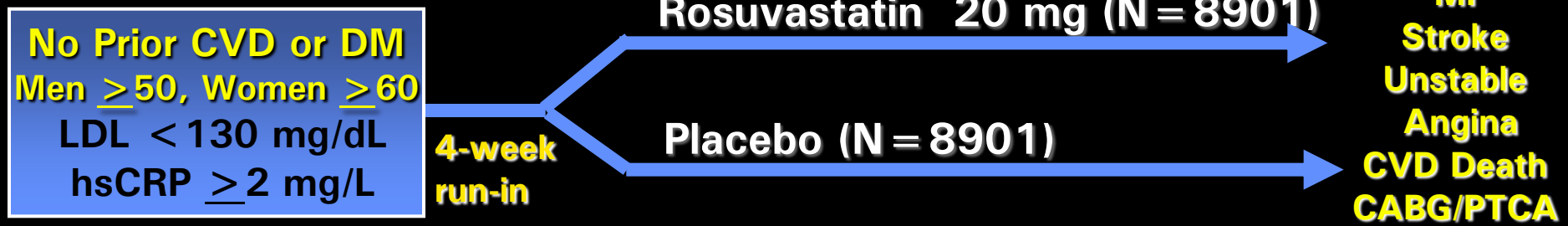
Circulation. 1999;100:230-235.

JUPITER
Trial Design

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



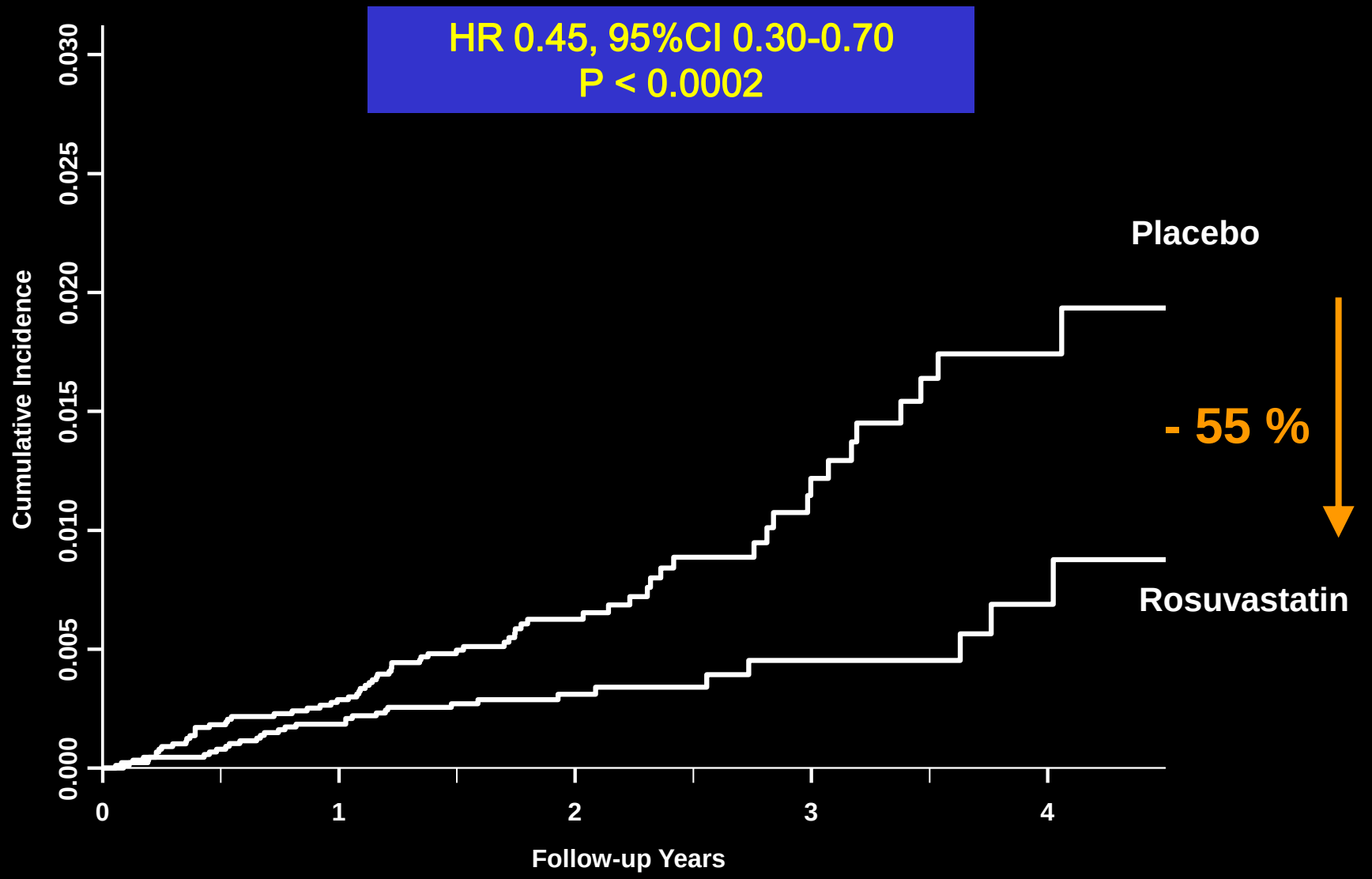
Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

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

JUPITER

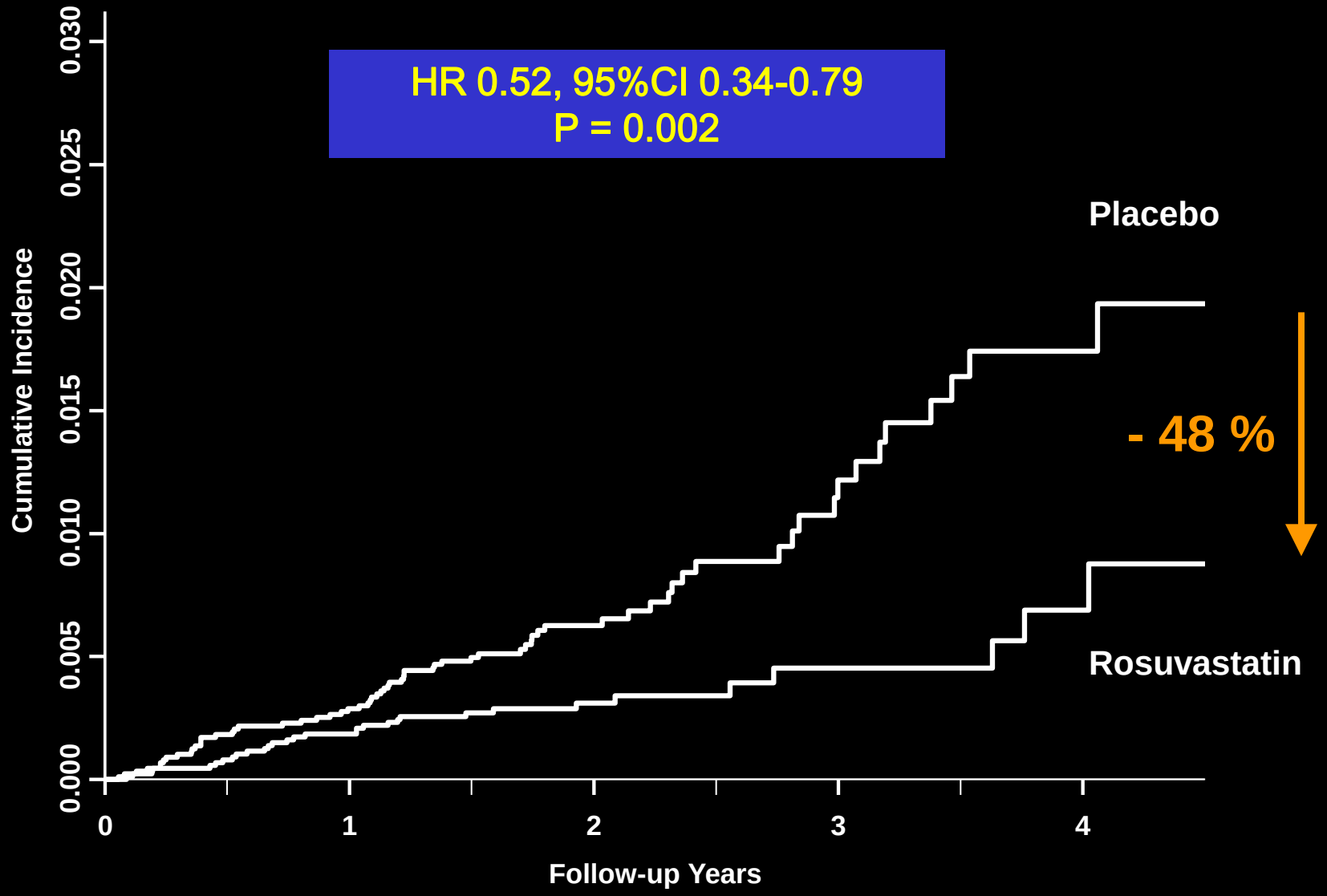
NEJM 2008;359:2195-2207

Fatal or Nonfatal Myocardial Infarction



JUPITER
Fatal or Nonfatal Stroke

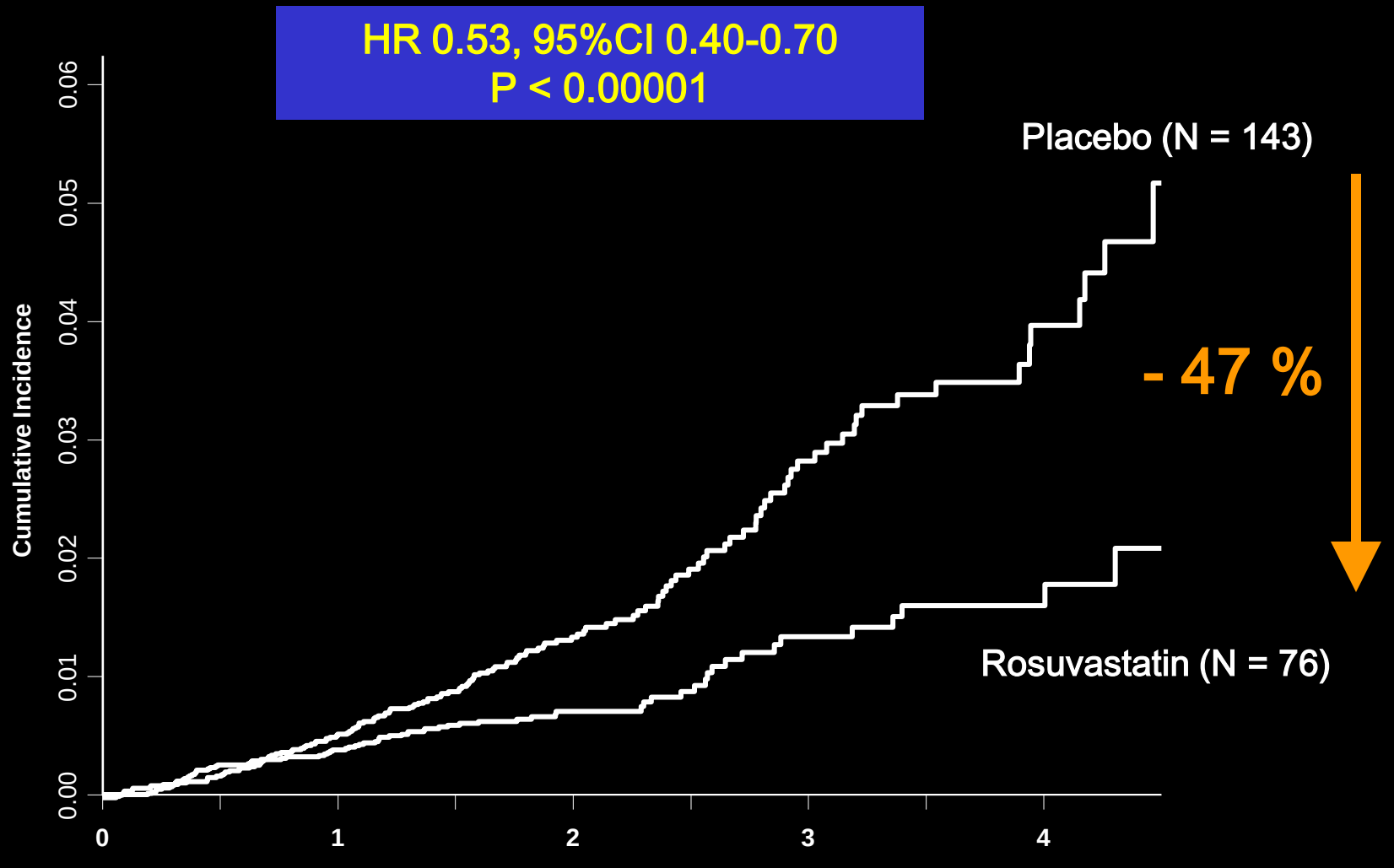
NEJM 2008;359:2195-2207



JUPITER

NEJM 2008;359:2195-2207

Arterial Revascularization / Unstable Angina

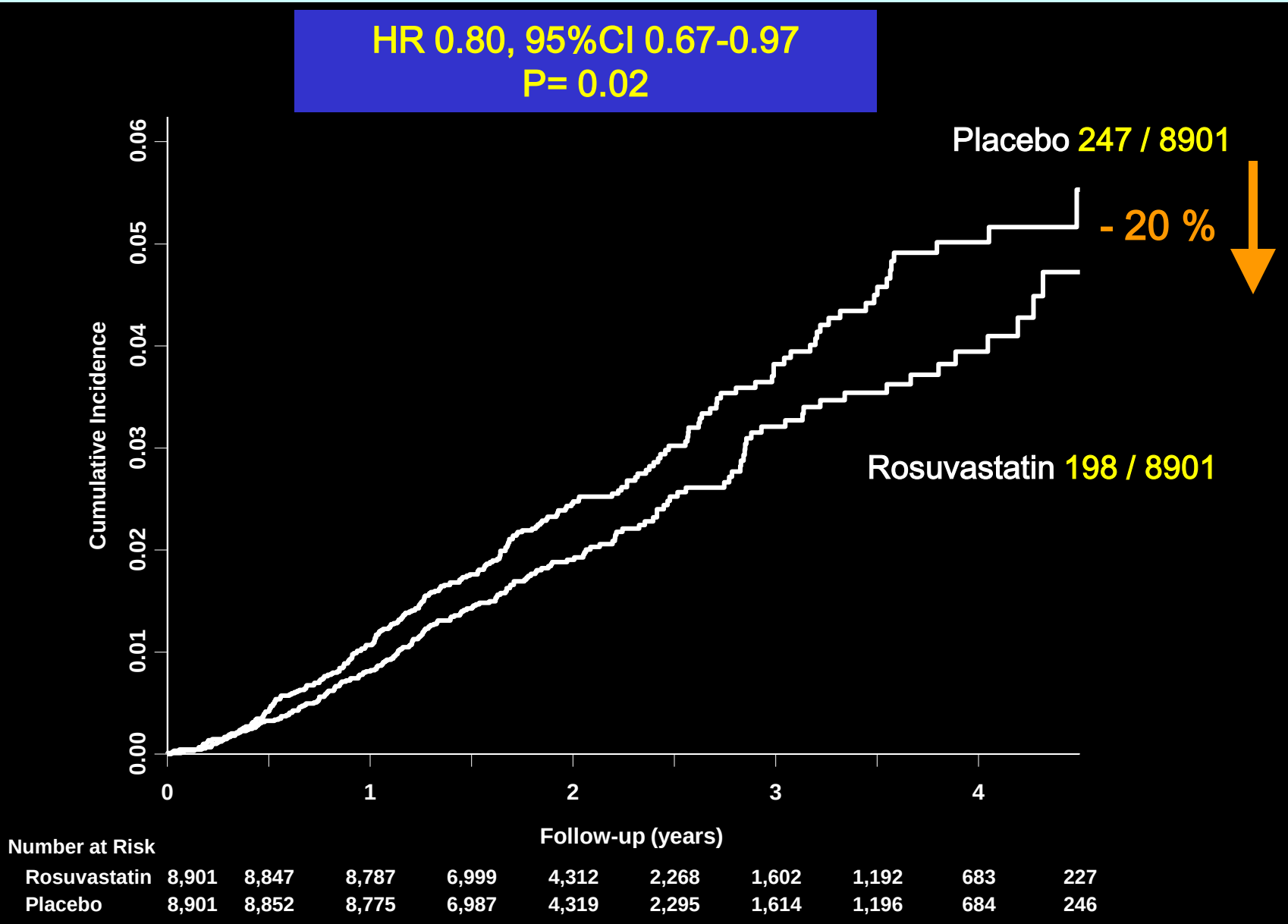


Number at Risk										
Rosuvastatin	8,901	8,640	8,426	6,550	3,905	1,966	1,359	989	547	158
Placebo	8,901	8,641	8,390	6,542	3,895	1,977	1,346	963	538	176

JUPITER

NEJM 2008;359:2195-2207

Secondary Endpoint – All Cause Mortality

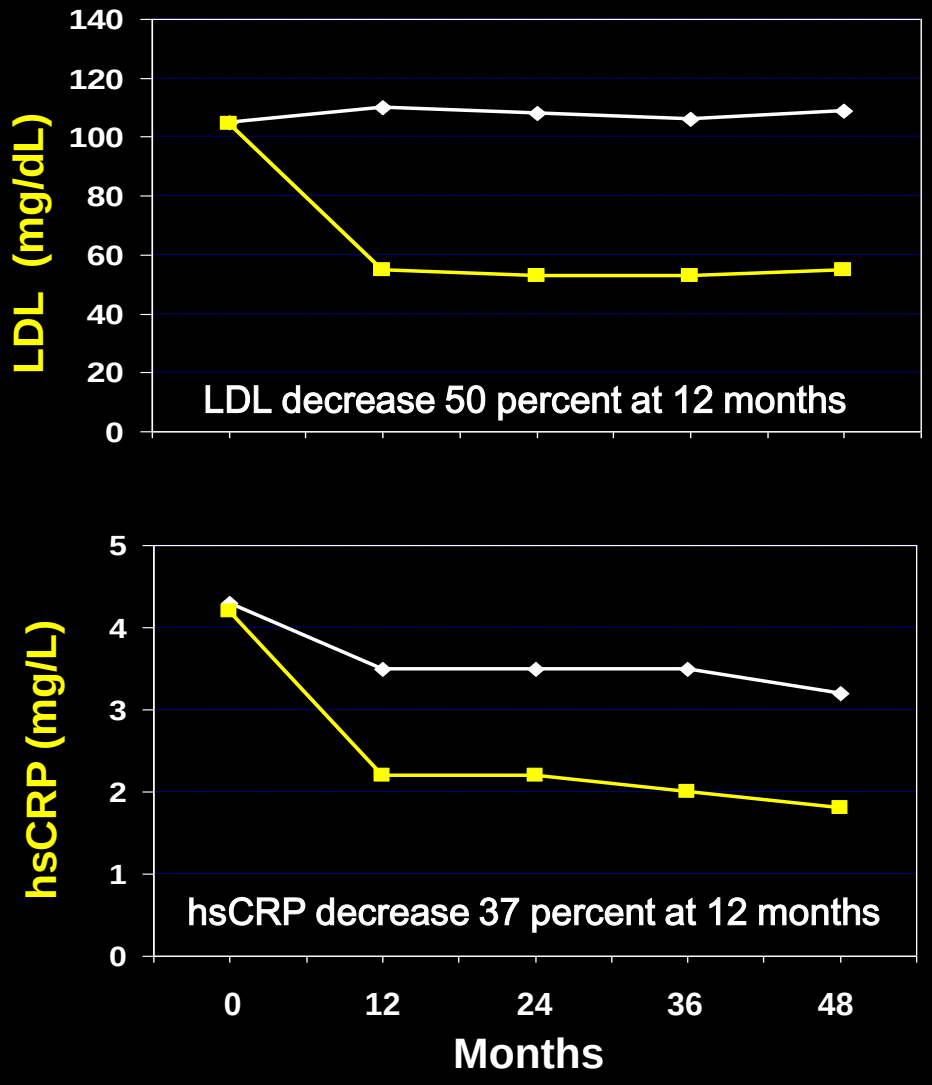


2009 Canadian Cardiovascular Society (CCS) Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult

		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

JUPITER
Achieved LDLC, Achieved hsCRP, or Both?



The Real Controversy:

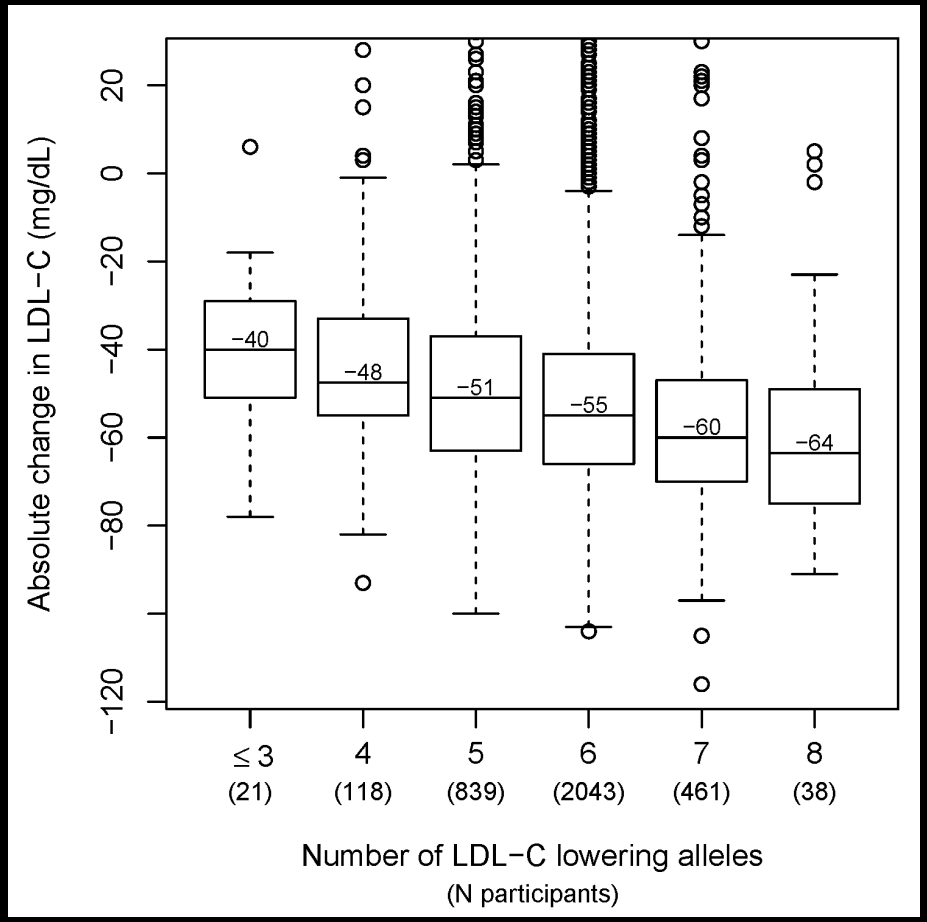
Is the large benefit observed in the JUPITER trial due to lipid lowering, to inflammation inhibition, or to a combination of these two processes?

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

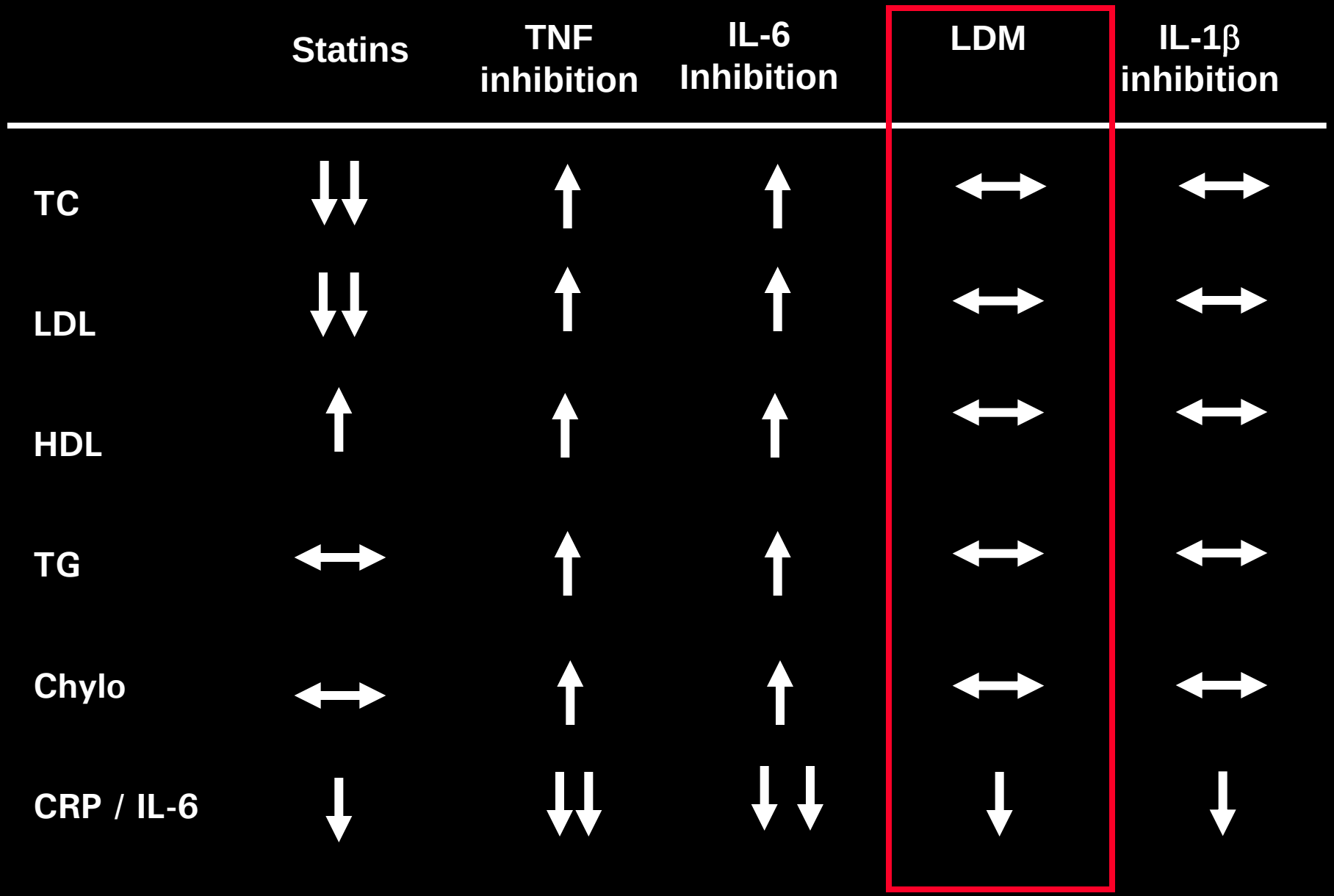
The genetic determinants of rousvastatin-induced CRP reduction do not predict rosuvastatin-induced LDL-C reduction



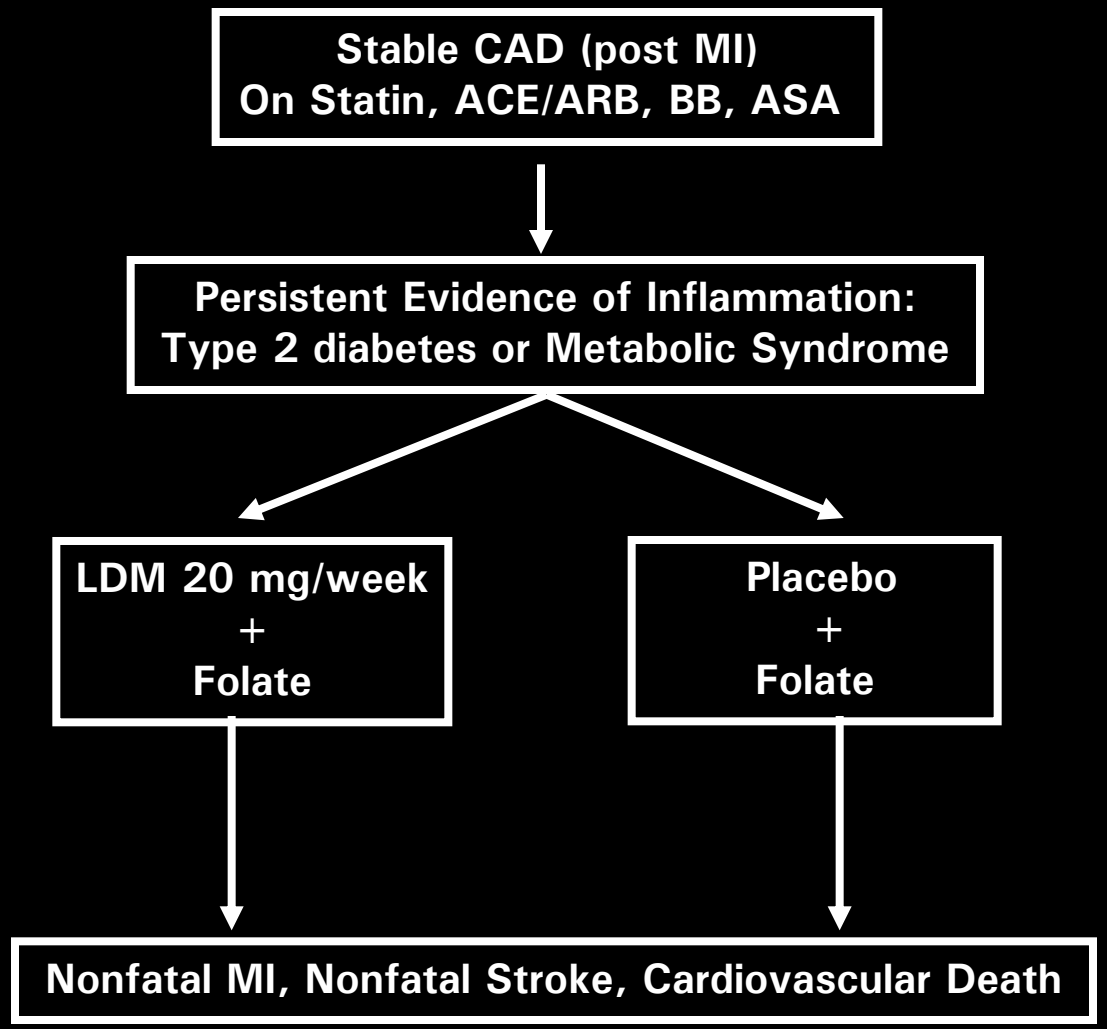
Chasman et al, 2012 Circulation Cardiovascular Genetics
Chu et al, 2012 Circulation Cardiovascular Genetics

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

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



Cardiovascular Inflammation Reduction Trial (CIRT)



Ridker PM. Thromb Haemost 2009

N = 7,000
FPFV October 2012

LDM and CVD: Observational Evidence

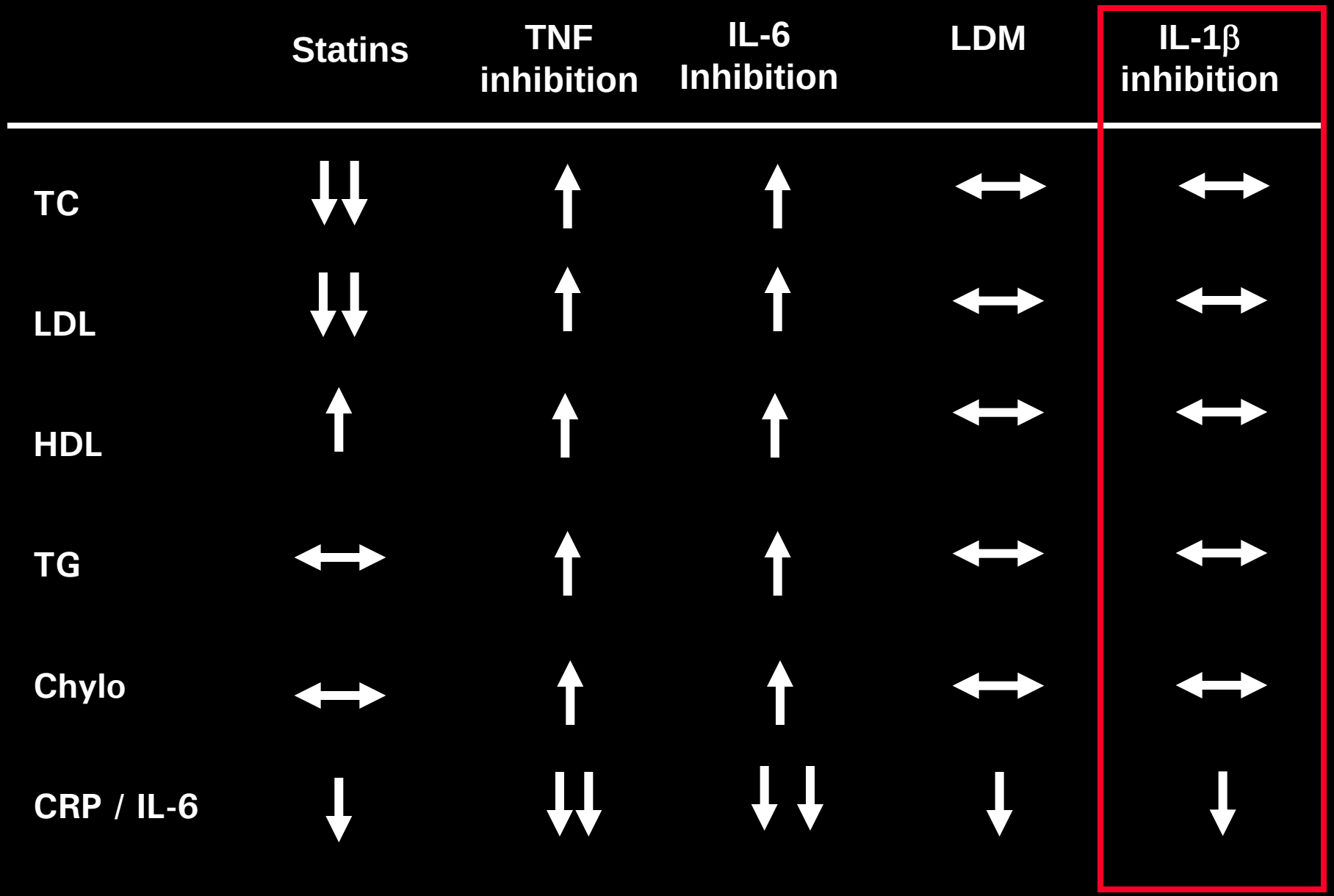
Cohort	Group	HR*	(95 % CI)	Endpoint	Exposure
Wichita	RA	0.4	(0.2 - 0.8)	Total Mortality	LDM
Choi 2002		0.3	(0.2 - 0.7)	CV Mortality	LDM
		0.4	(0.3 – 0.8)	CV Mortality	LDM < 15 mg/wk
Netherlands	RA	0.3	(0.1 – 0.7)	CVD	LDM only
van Helm 2006		0.2	(0.1 – 0.5)	CVD	LDM + SSZ
		0.2	(0.1 – 1.2)	CVD	LDM + HCQ
		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

Cardiovascular Inflammation Reduction Trial (CIRT)

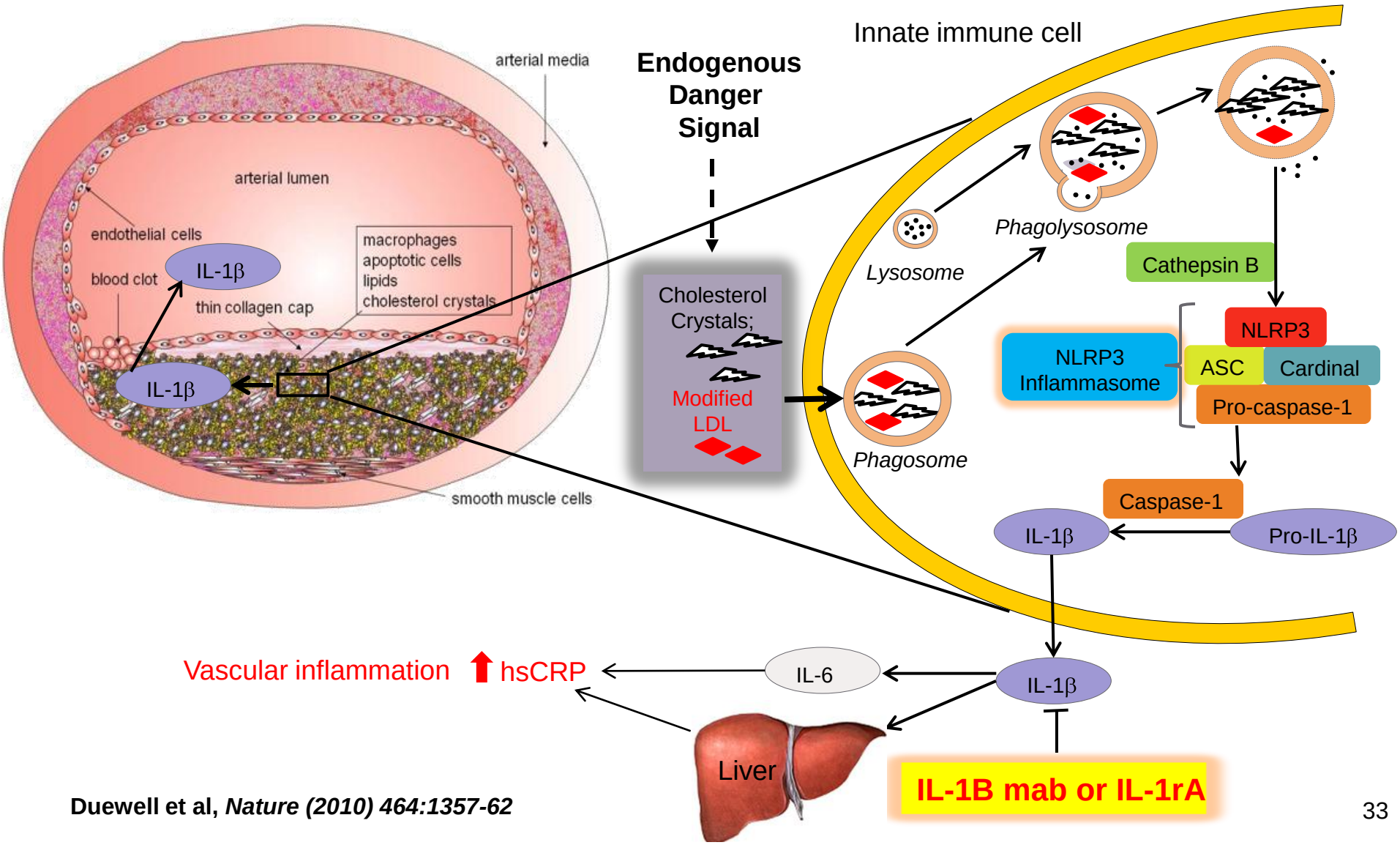
Primary Aim

- To directly test the inflammatory hypothesis of atherothrombosis by evaluating in a randomized, double-blind, placebo-controlled trial whether LDM given at a target dose of 20 mg po weekly over a three to four 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.

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



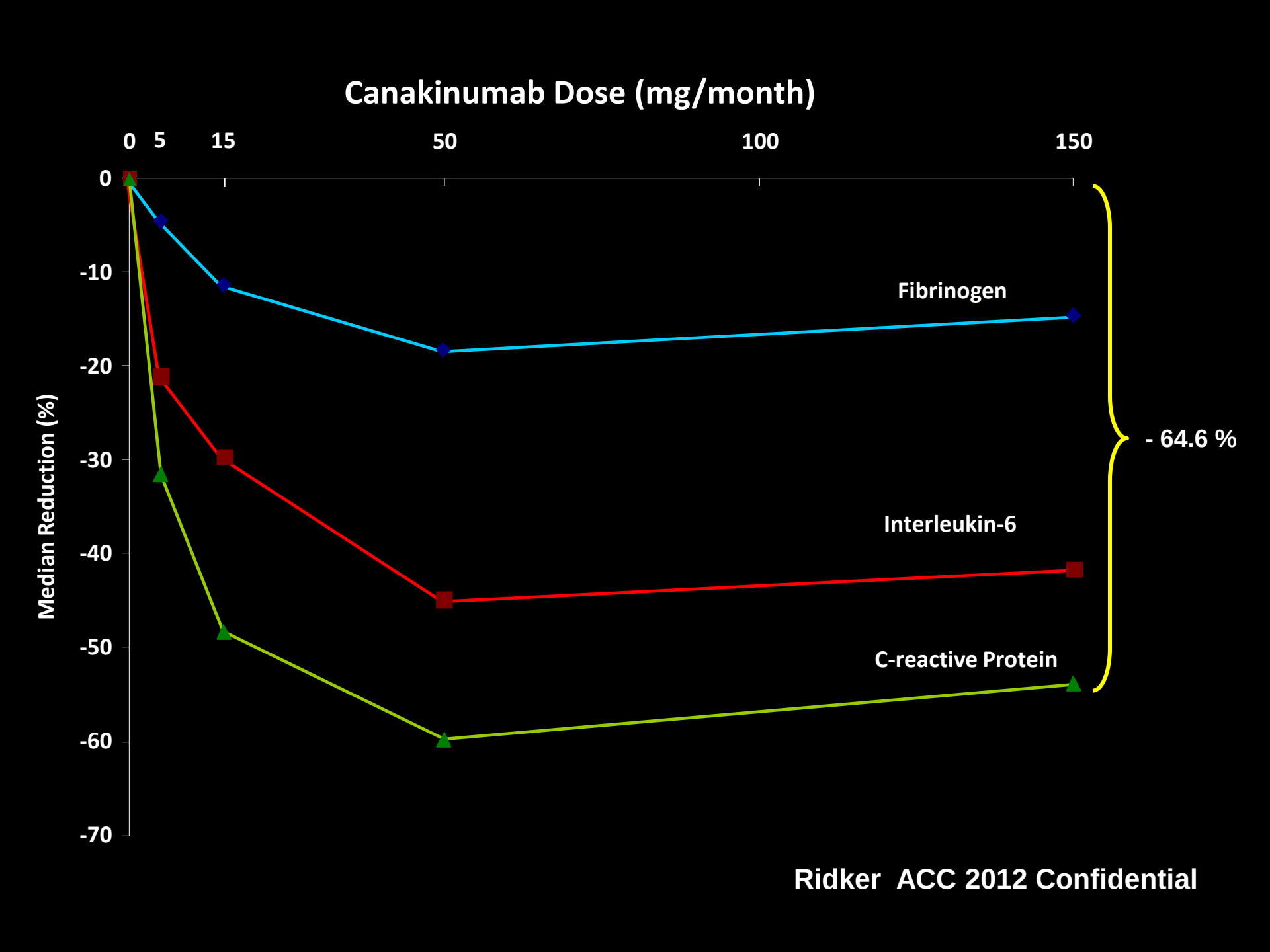
Cholesterol crystals activate the caspase-1-activating NLRP3 inflammasome to generate IL-1β and initiate atherosclerosis



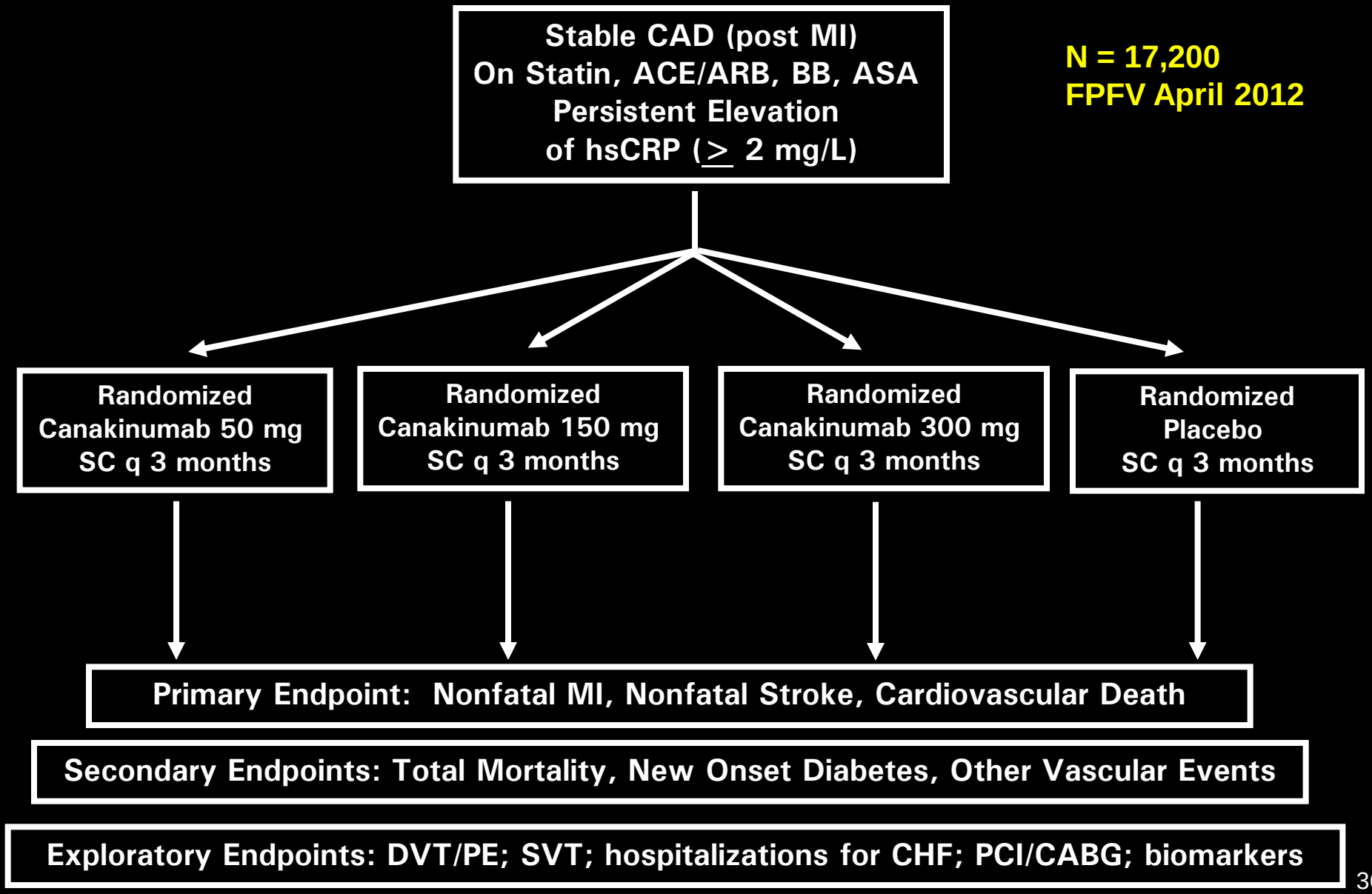
Duewell et al, *Nature (2010) 464:1357-62*

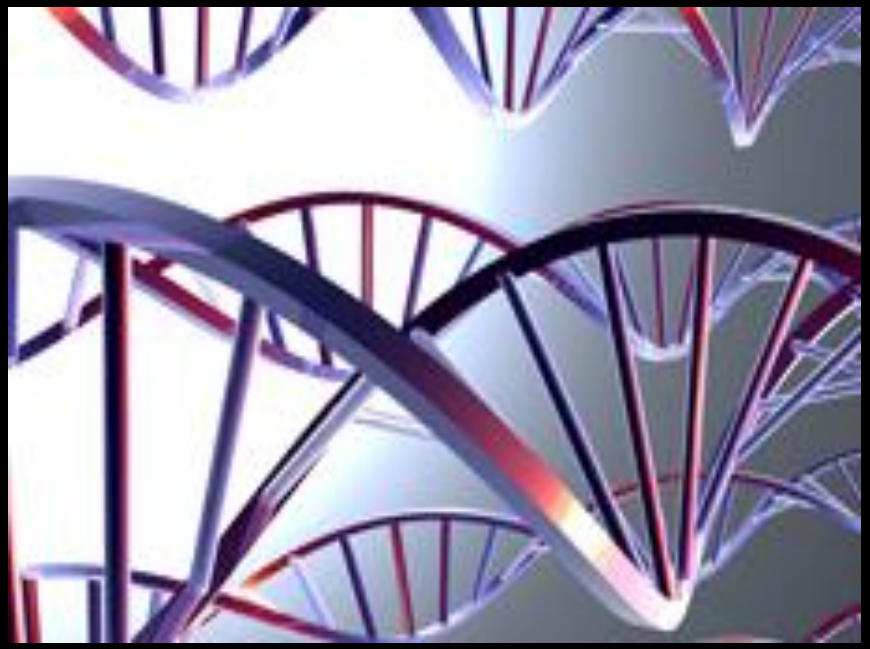
Canakinumab (Ilaris, Novartis)

- **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**


Canakinumab Dose (mg/month)
0
5
15
50
100
150
0
-10
-20
-30
-40
-50
-60
-70
Median Reduction (%)
Fibrinogen
Interleukin-6
C-reactive Protein
- 64.6 %
Ridker ACC 2012 Confidential

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

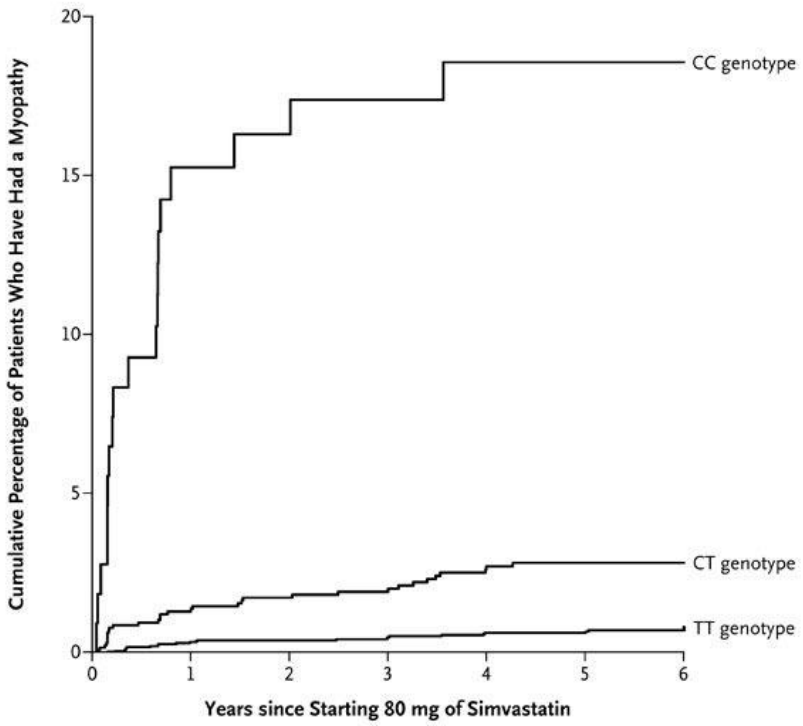




Will genetic screening play a role in patient focused thrombosis care?

Will pharmacogenetics matter for cardiovascular disease?

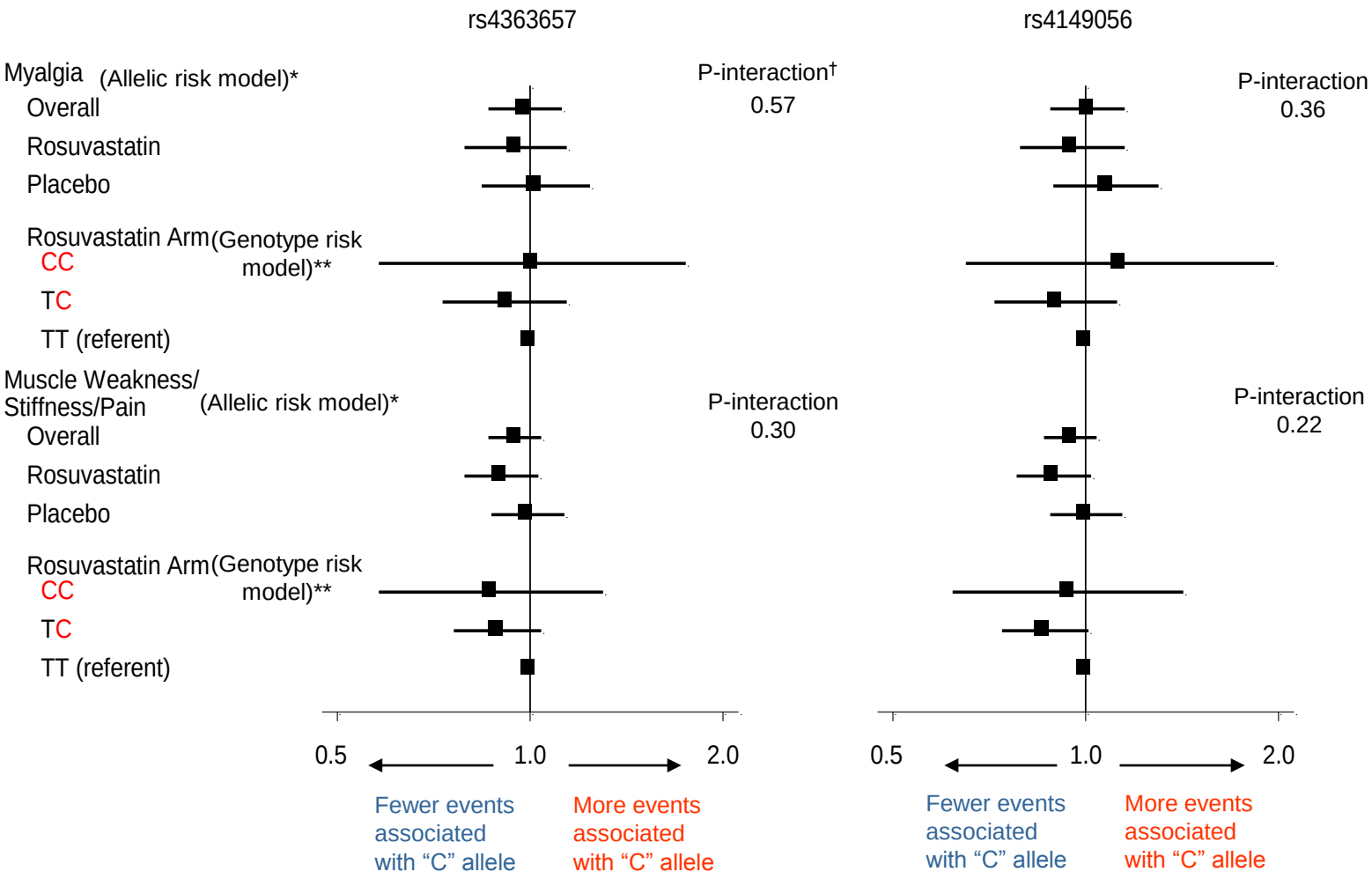
Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, According to SLCO1B1 rs4149056 Genotype



Genotype	Population Frequency	Cumulative No. and Percentages with Myopathy							
		Year 1				Year 5			
				Attributable to gentoype				Attributable to gentoype	
		no.	%	*no.*	*% of total*	*no.*	%	*no.*	*% of total*
TT	0.730	12	0.34	0	0	21	0.63	0	0
CT	0.249	17	1.38	12.8	75	32	2.83	24.9	78
CC	0.021	16	15.25	15.6	98	19	18.55	18.4	97
All genotypes	1.000	45	0.91	28.4	63	72	1.56	43.3	60

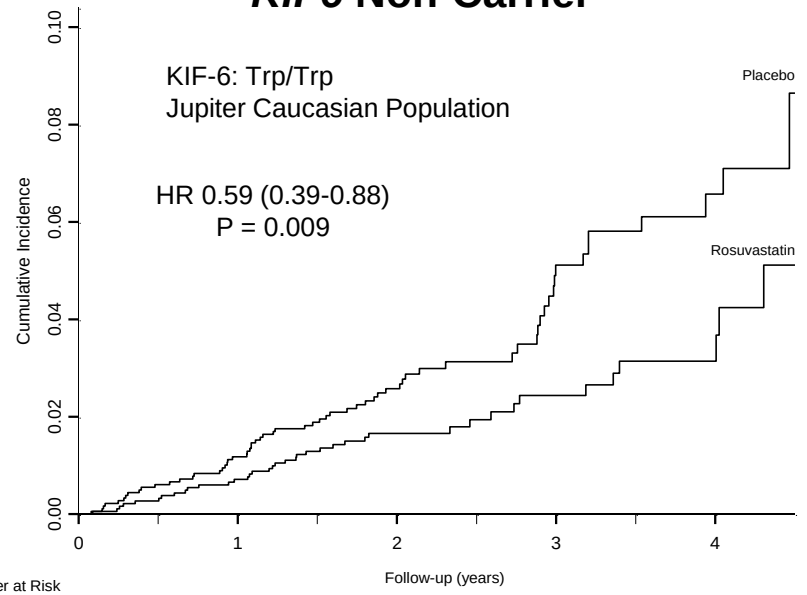
The SEARCH Collaborative Group. N Engl J Med 2008;359:789-799

Risk of muscular complaints by treatment groups and *SLCO1B1* genotypes



JUPITER: Rosuvastatin is Equally Effective at Lowering Vascular Risk Among those With and Without the *KIF6* Polymorphism

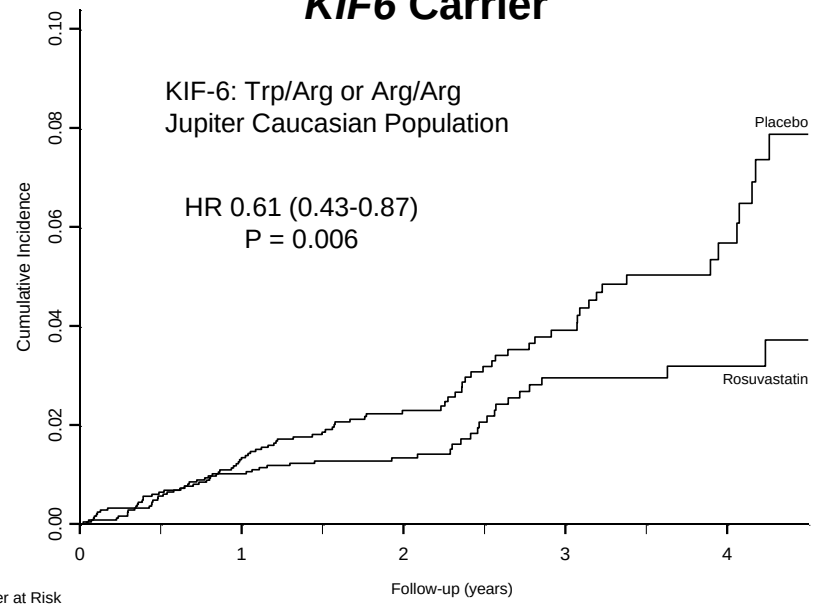
KIF6 Non-Carrier



Number at Risk

Rosuvastatin	1,883	1,829	1,779	1,469	1,101	652	494	367	181	52
Placebo	1,834	1,779	1,724	1,435	1,066	602	444	328	188	53

KIF6 Carrier



Number at Risk

Rosuvastatin	2,521	2,448	2,379	1,982	1,485	834	630	452	258	73
Placebo	2,543	2,461	2,379	1,971	1,479	885	669	472	254	83

Similar LDL and hsCRP reduction by genotype
Similar absolute event rates by genotype
Similar relative risk reduction by genotype

Circ CV Genetics 2011

Some Thoughts About Eric Green's Density Maps
On the Speed of Translation to Practice

1. Don't be discouraged. It takes a long time to change practice even when randomized trials exist.

2. Sure, there are bumps, potholes, and u-turns on the Translational Highway, but were else are you going to drive?

3. A true killer app would be nice, but we may not need that since the "average" patient may not be what this is all about. If the cost of screening falls far enough, we don't need a homerun for all patients, just a clear benefit for some, even if they are rare individuals.

4. It really matters for parents and kids

It must be considered that there is nothing more difficult to carry out, nor more doubtful of success, nor more dangerous to handle, than to initiate a new order of things. For the reformer has enemies in all those who profit by the old order, and only lukewarm defenders in all those who would profit by the new order, this lukewarmness arriving partly from fear and partly from the incredulity of mankind, who do not believe in anything new until they have had an actual experience of it.

Nicolo Machiavelli 1513

Chasman et al,
Atherosclerosis 2008

Differential effects of aspirin on vascular outcomes according to polymorphism in the Lp(a) gene