

# Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease and Lung Cancer



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Paul M Ridker, MD, MPH

Eugene Braunwald Professor of Medicine  
Brigham and Women's Hospital,  
Harvard Medical School, Boston MA, USA



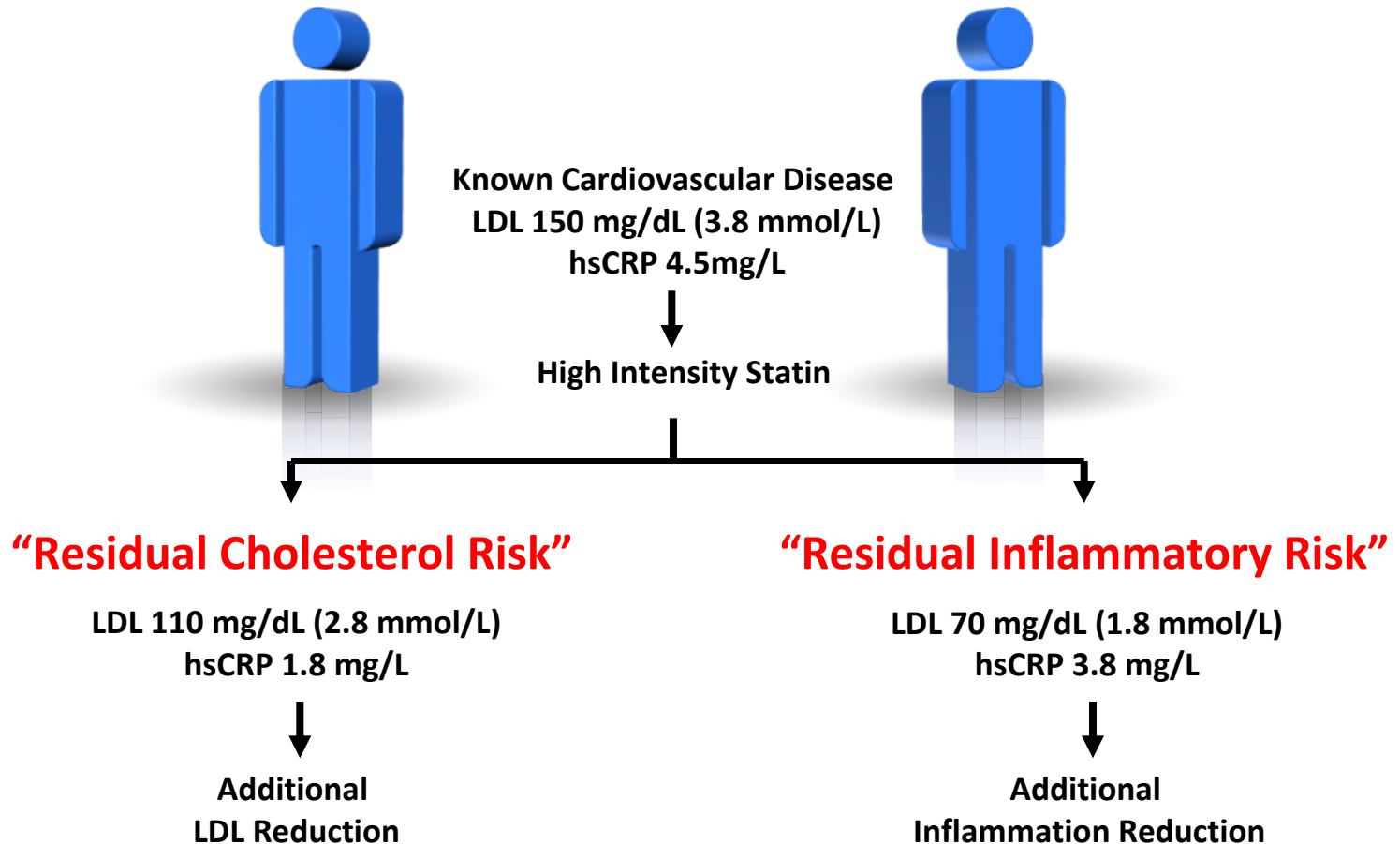
on behalf of the worldwide investigators and participants in the  
**Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)**

# Declaration of interest

- Research contracts (Novartis)
- Consulting/Royalties/Owner/ Stockholder of a healthcare company (Dr Ridker is listed as a coninventor on patents related to the use of inflammatory biomarker in cardiovascular disease.)

# Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. *Eur Heart J* 2016;37:1720-22

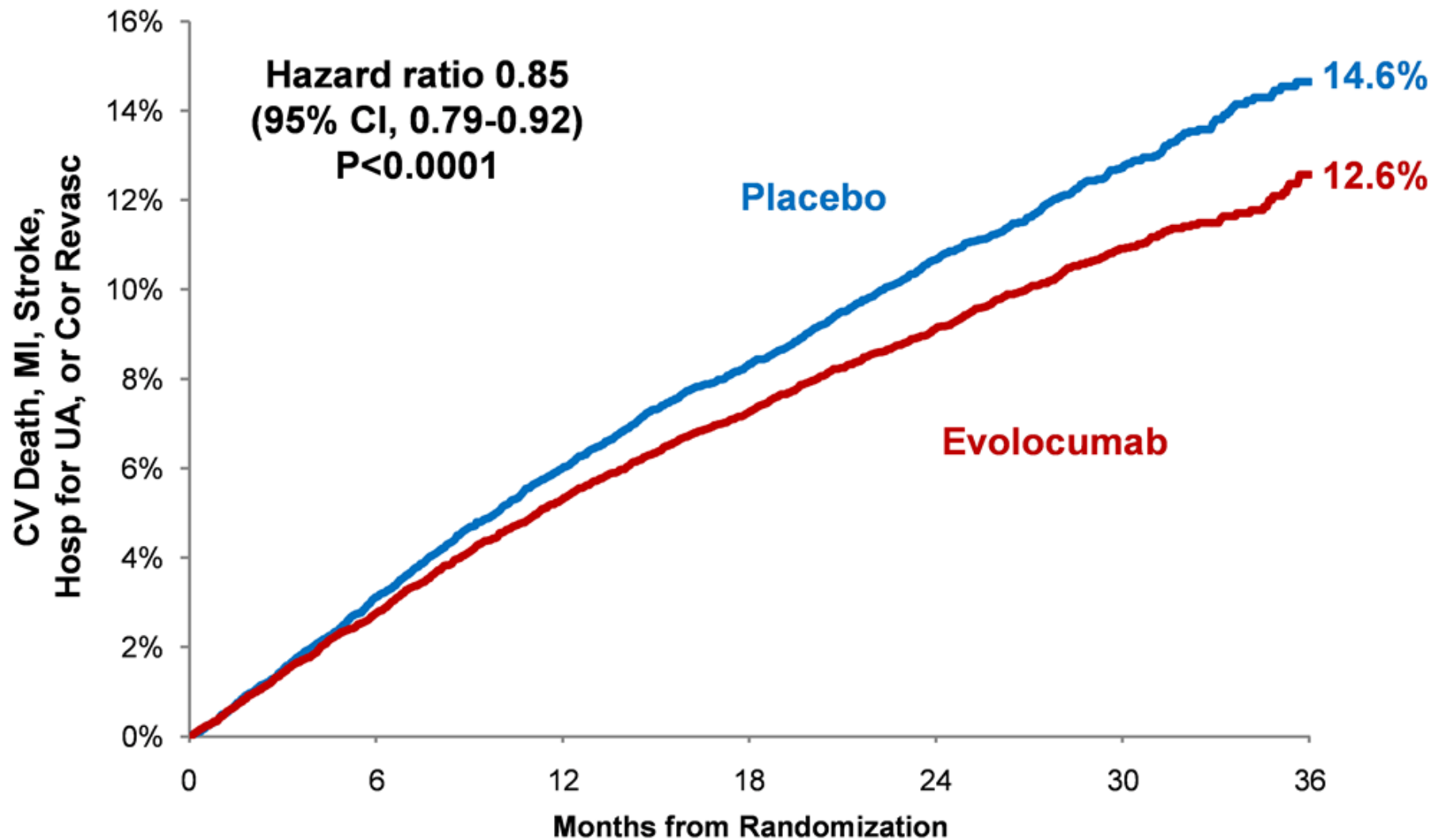


**IMPROVE-IT : Ezetimibe 6% RRR**  
**FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR**

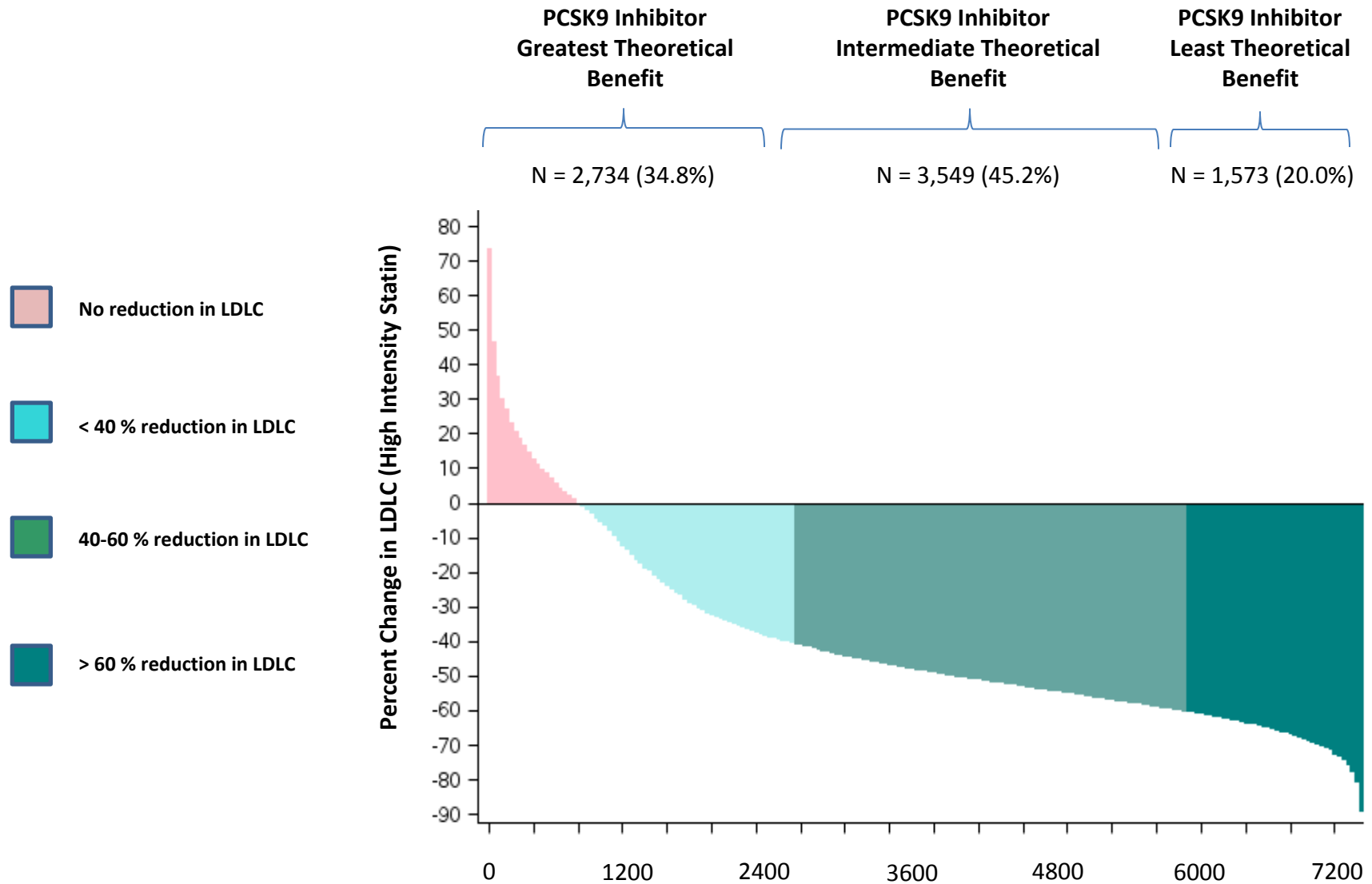
**No Prior Proof of Concept**



# Primary Endpoint

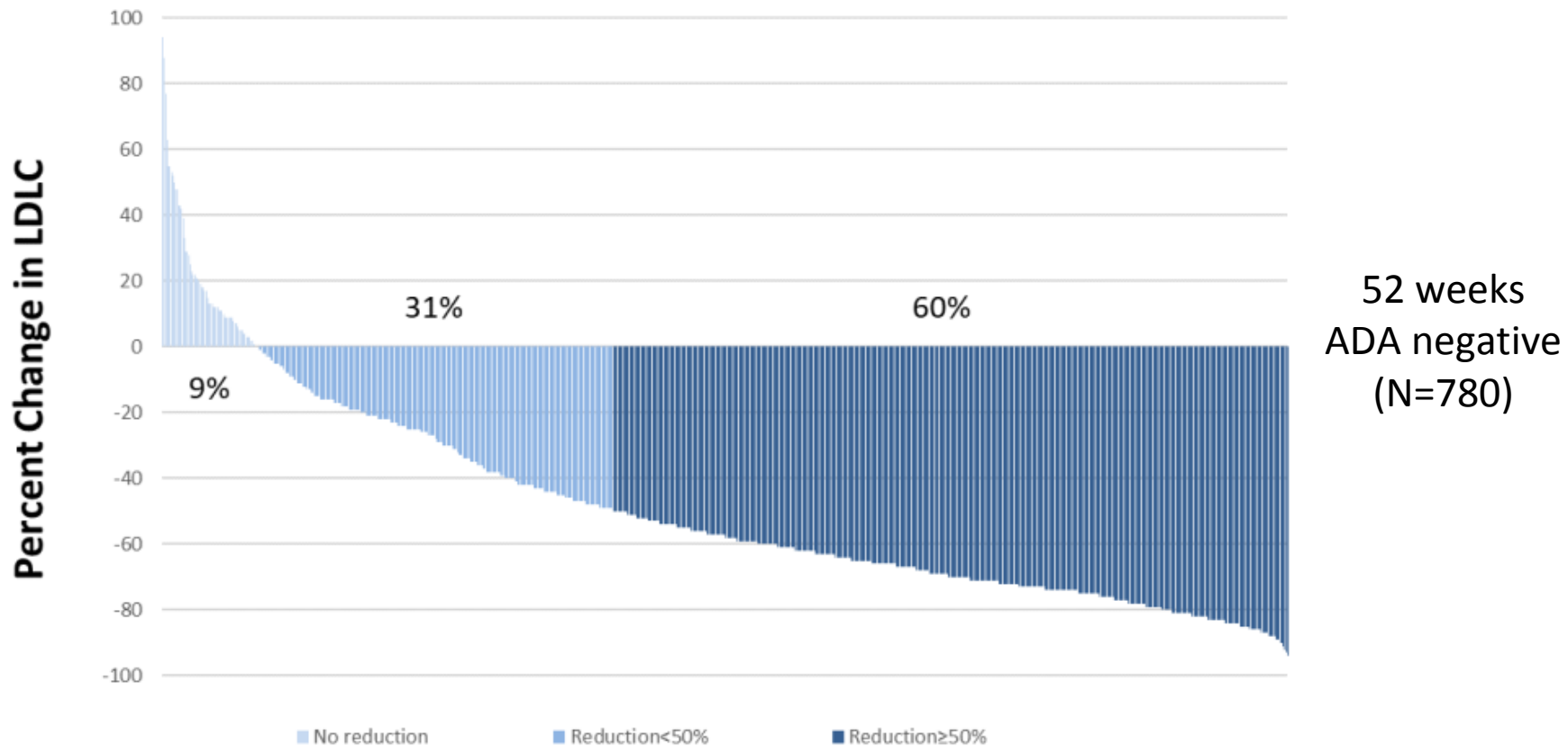


# Percent Reduction in LDL Response to High Intensity Statin Therapy: Implications for PCSK9 Prescription



# The SPIRE Bococizumab Lipid Lowering Trials :

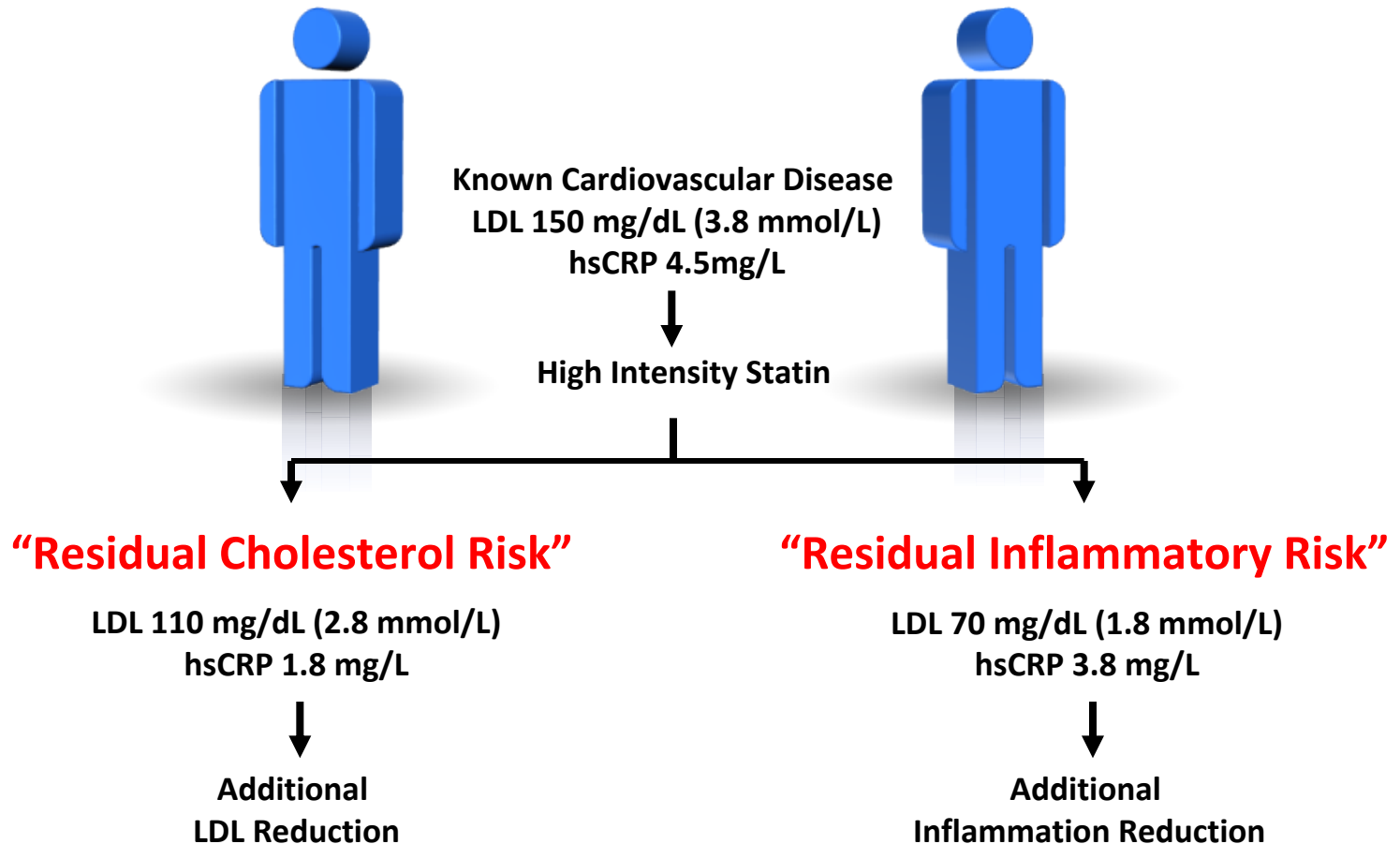
## Wide Individual Variation in Percent Change in LDLC at 52 Weeks with Bococizumab, Even Among Those Who Are Antidrug Antibody Negative\*



\* Analysis excludes non-compliant participants

# Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. *Eur Heart J* 2016;37:1720-22

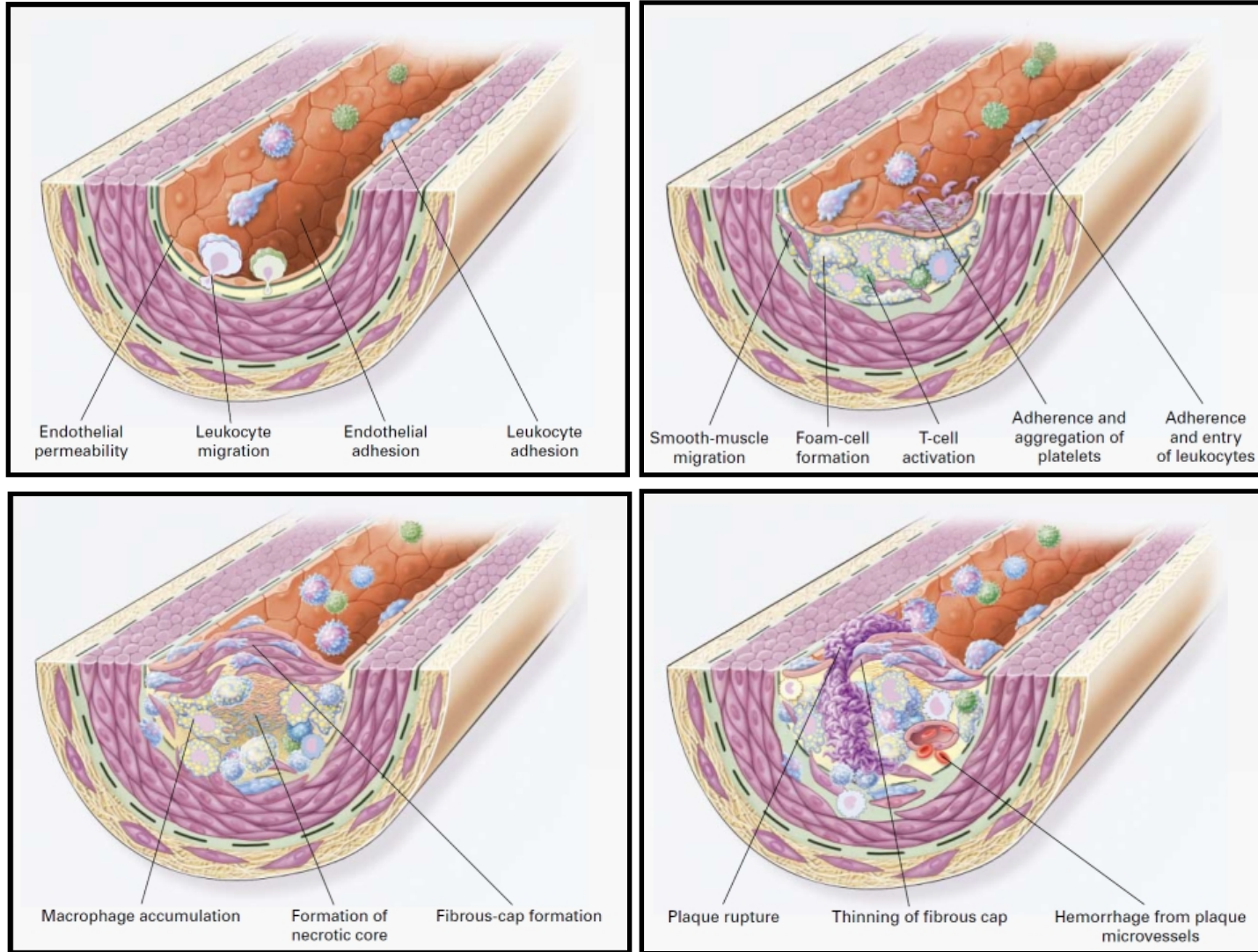


**IMPROVE-IT : Ezetimibe 6% RRR**  
**FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR**

**No Prior Proof of Concept**

# ATHEROSCLEROSIS — AN INFLAMMATORY DISEASE

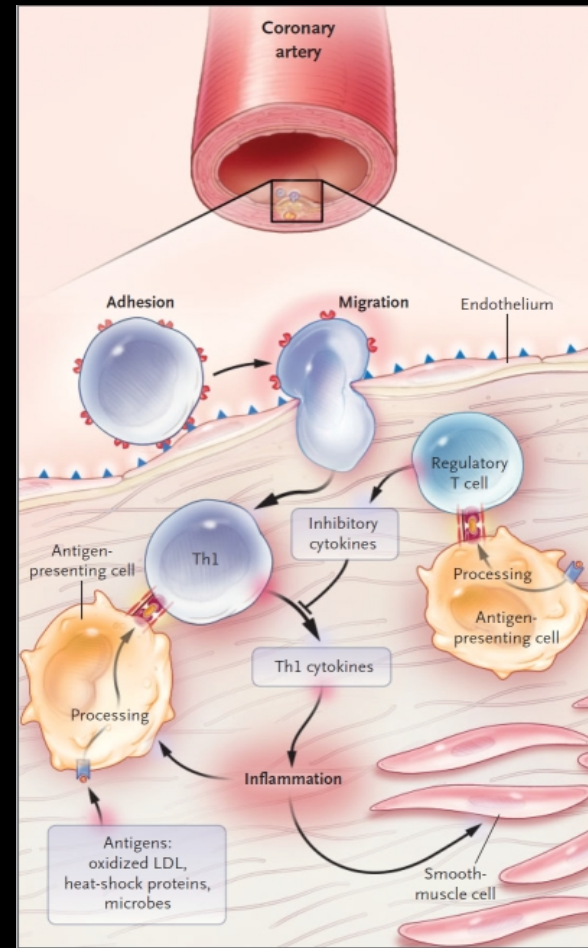
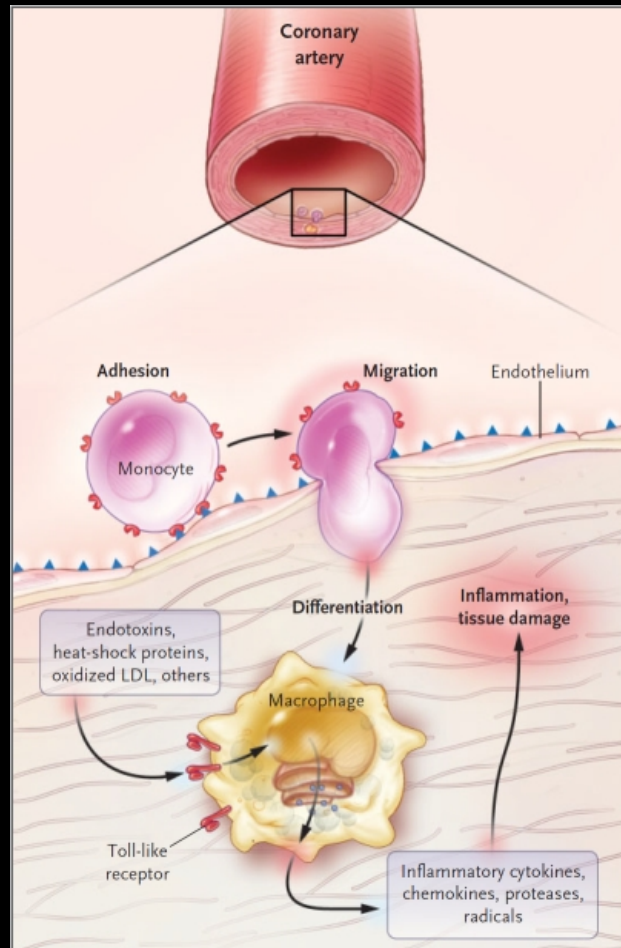
RUSSELL ROSS, PH.D.



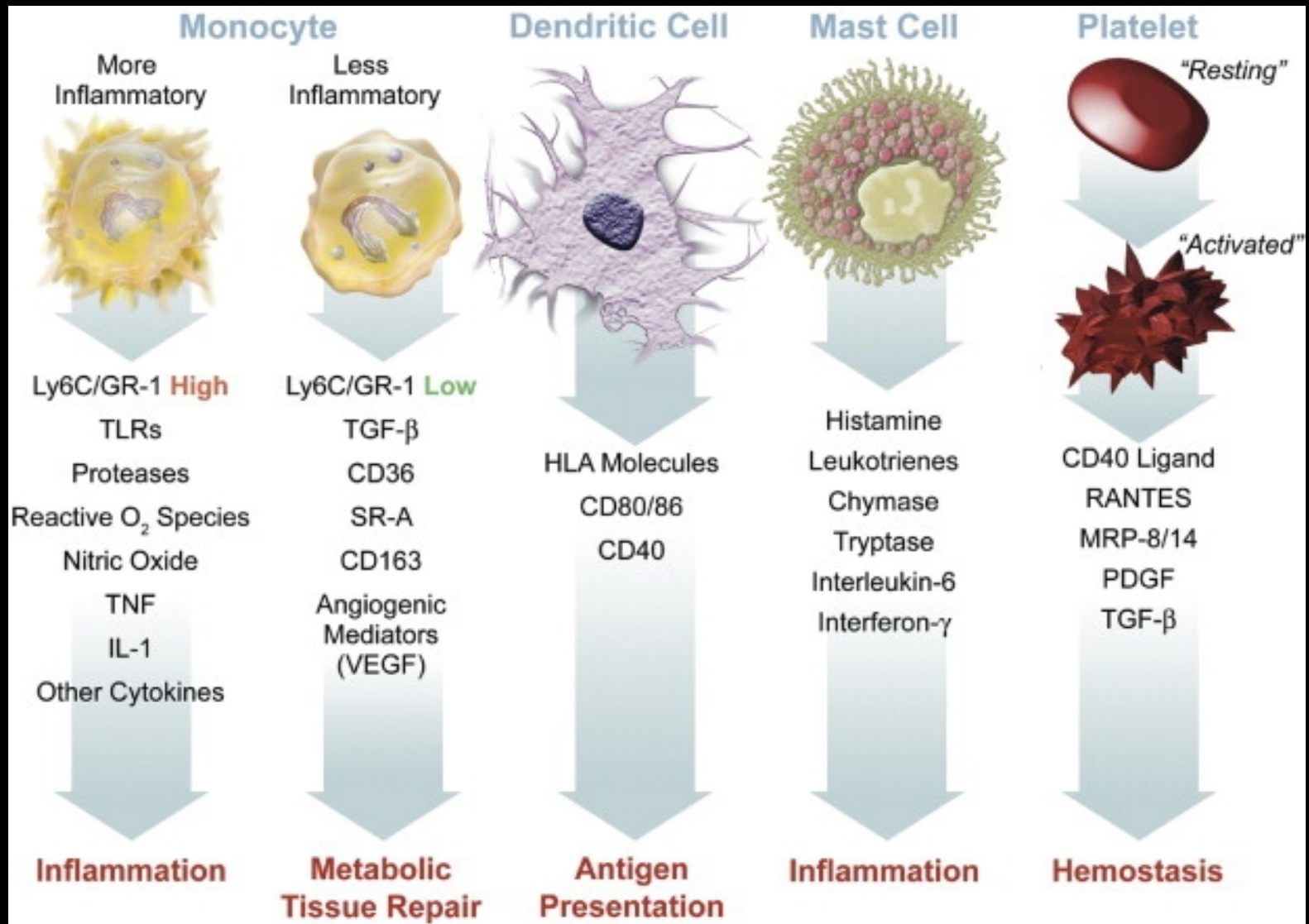


# Inflammation, Atherosclerosis, and Coronary Artery Disease

Göran K. Hansson, M.D., Ph.D.



# Inflammation in atherosclerosis: from pathophysiology to practice



# The New England Journal of Medicine

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VOLUME 336

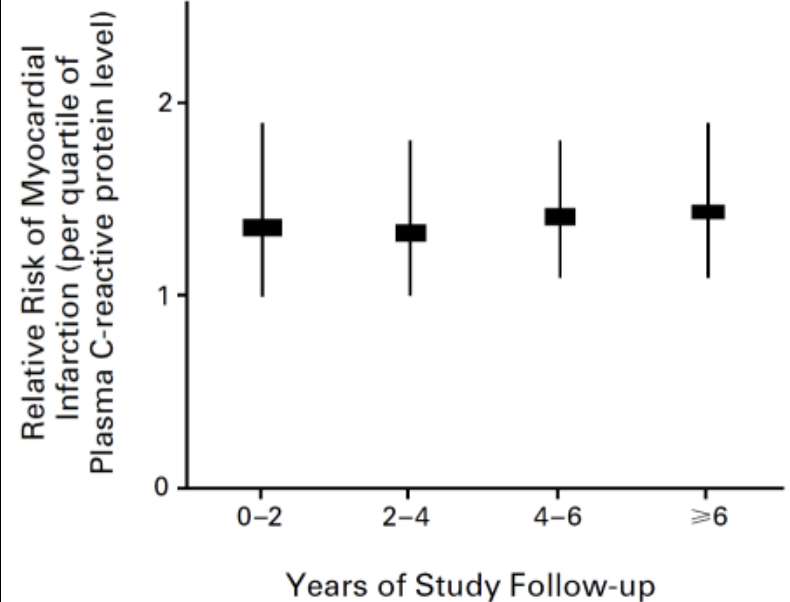
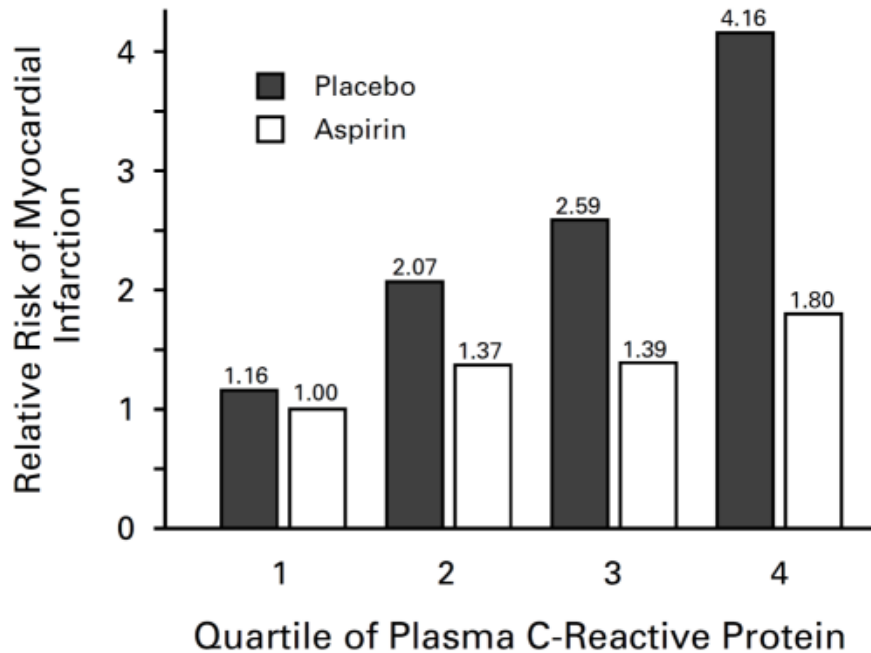
APRIL 3, 1997

NUMBER 14

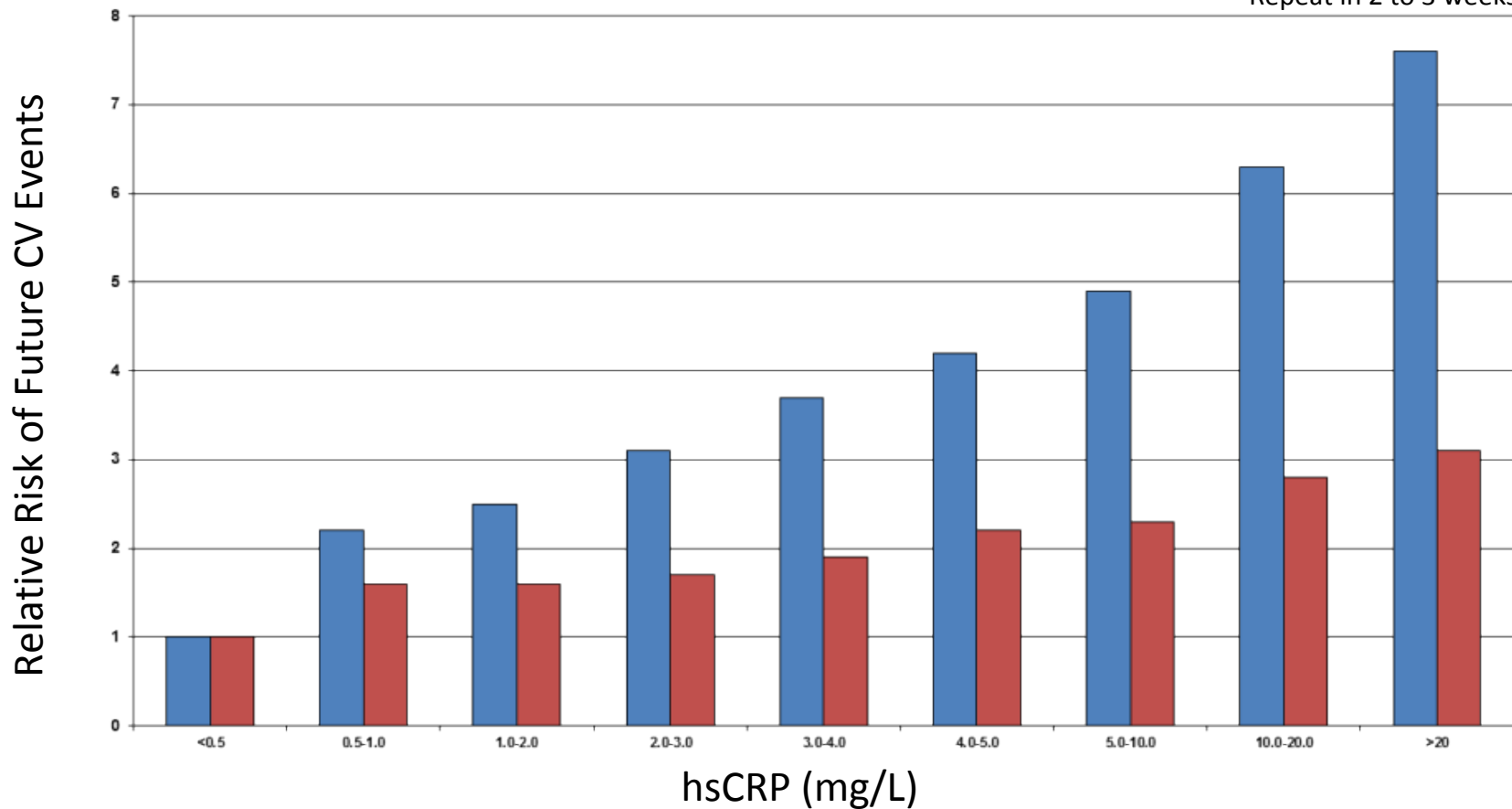
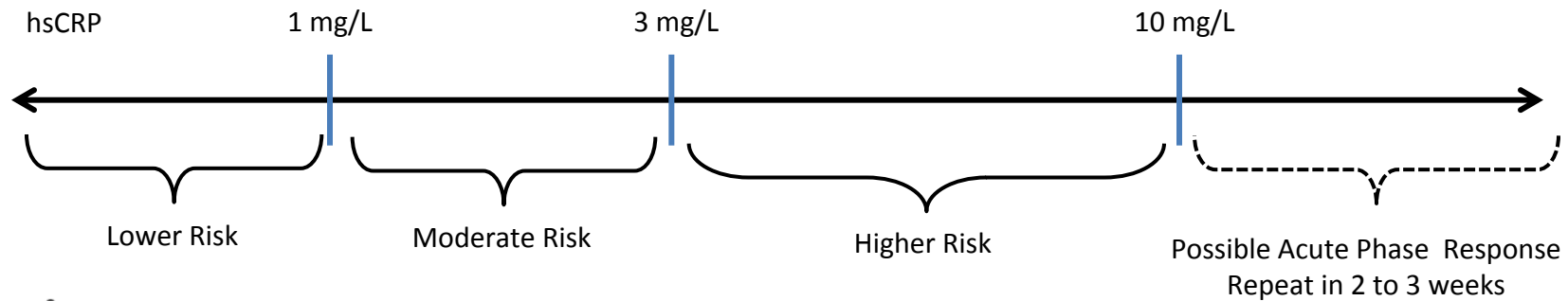


## INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

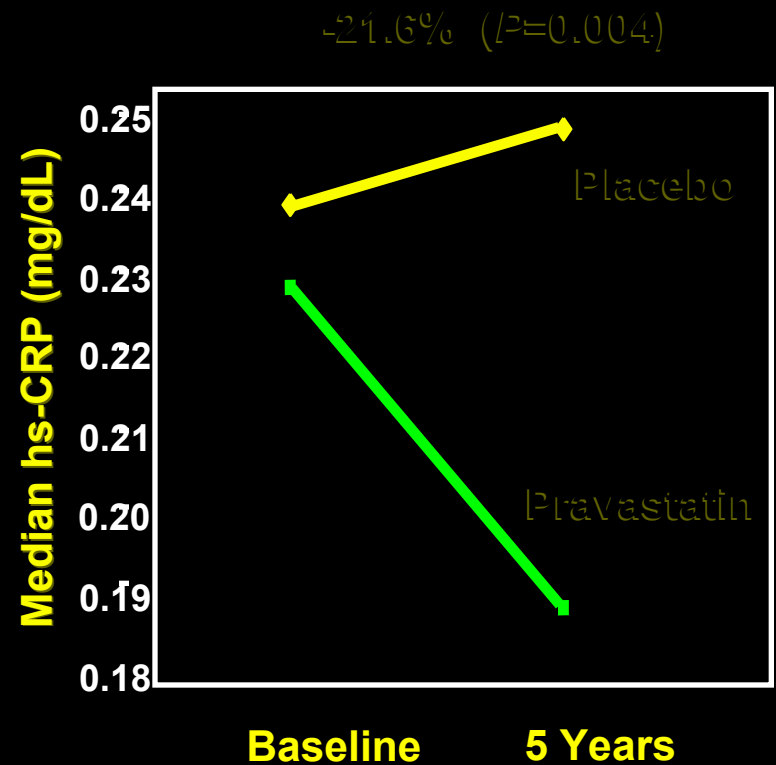
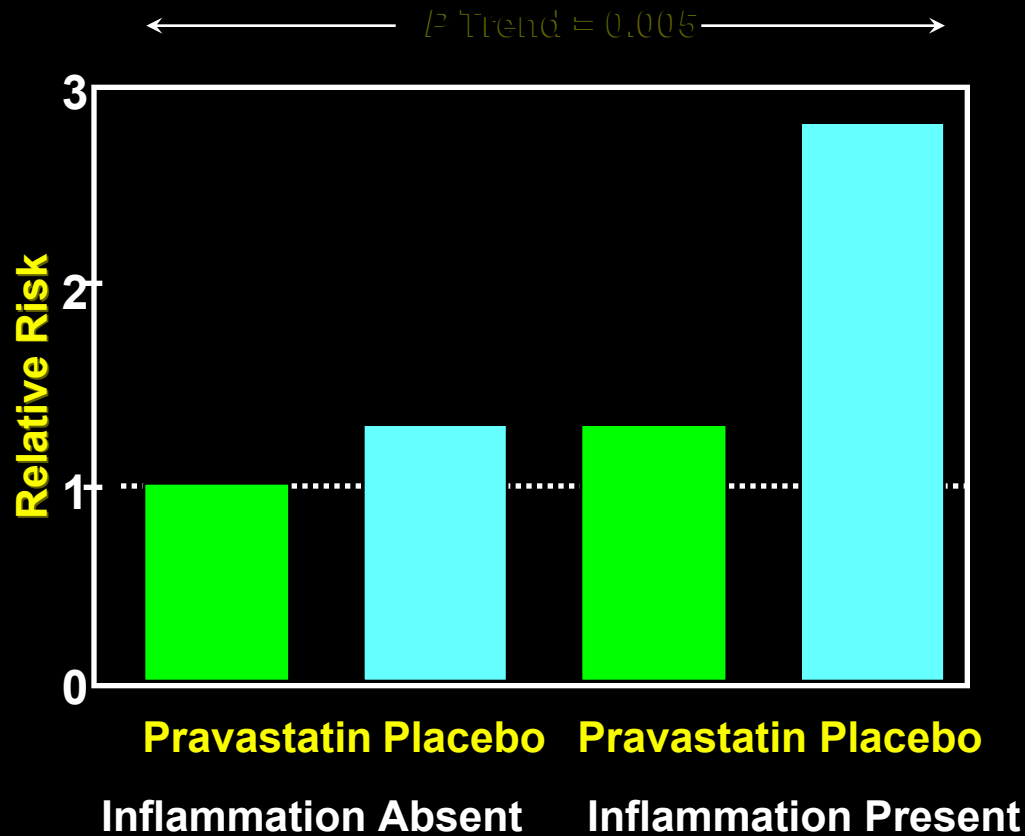
PAUL M. RIDKER, M.D., MARY CUSHMAN, M.D., MEIR J. STAMPFER, M.D., RUSSELL P. TRACY, PH.D.,  
AND CHARLES H. HENNEKENS, M.D.



# High Sensitivity C-Reactive Protein (hsCRP) : A Test In Context

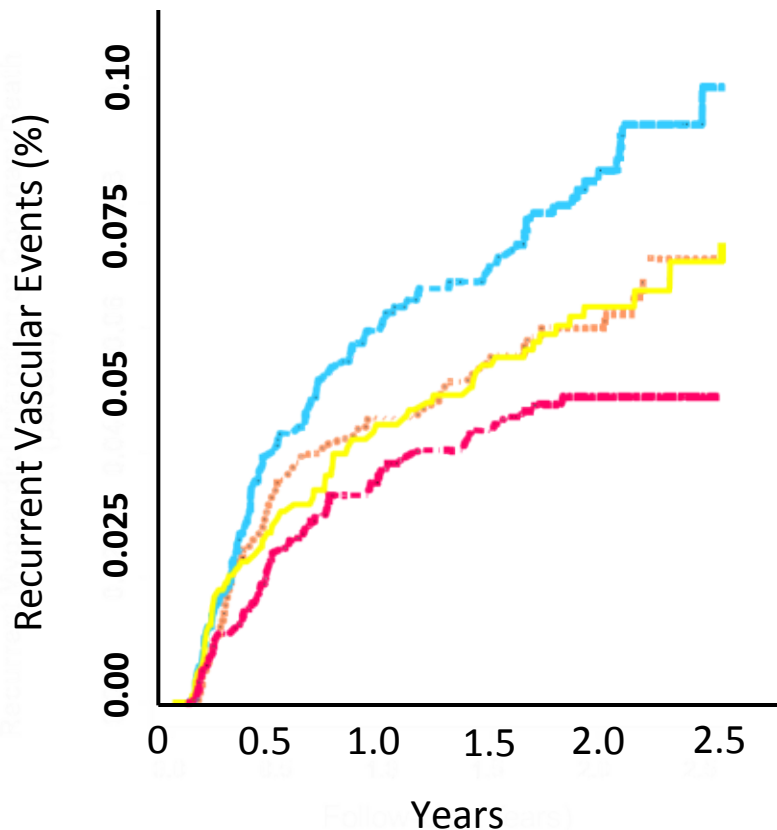


# Inflammation, Statin Therapy, and hsCRP: Initial Observations



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

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



### PROVE-IT

Ridker et al, NEJM 2005;352:20-8

■ LDL >70 mg/dL  
hsCRP > 2mg/L

Neither Goal  
Achieved

■ LDL <70 mg/dL  
hsCRP > 2mg/L

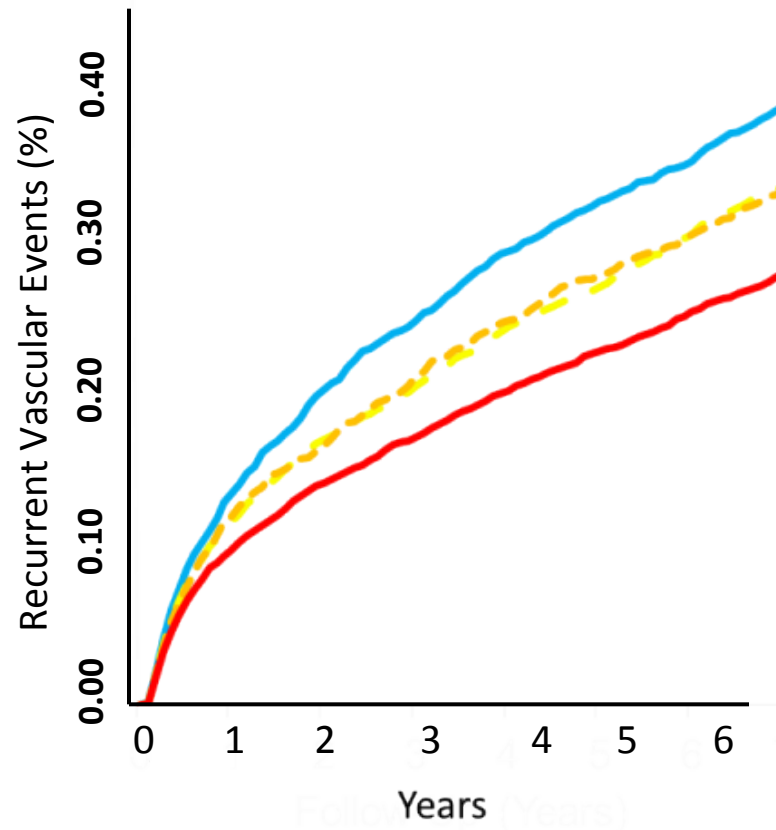
LDL Goal  
Achieved

■ LDL > 70 mg/dL  
hsCRP < 2mg/L

hsCRP Goal  
Achieved

■ LDL <70 mg/dL  
hsCRP < 2mg/L

Dual Goals  
Achieved



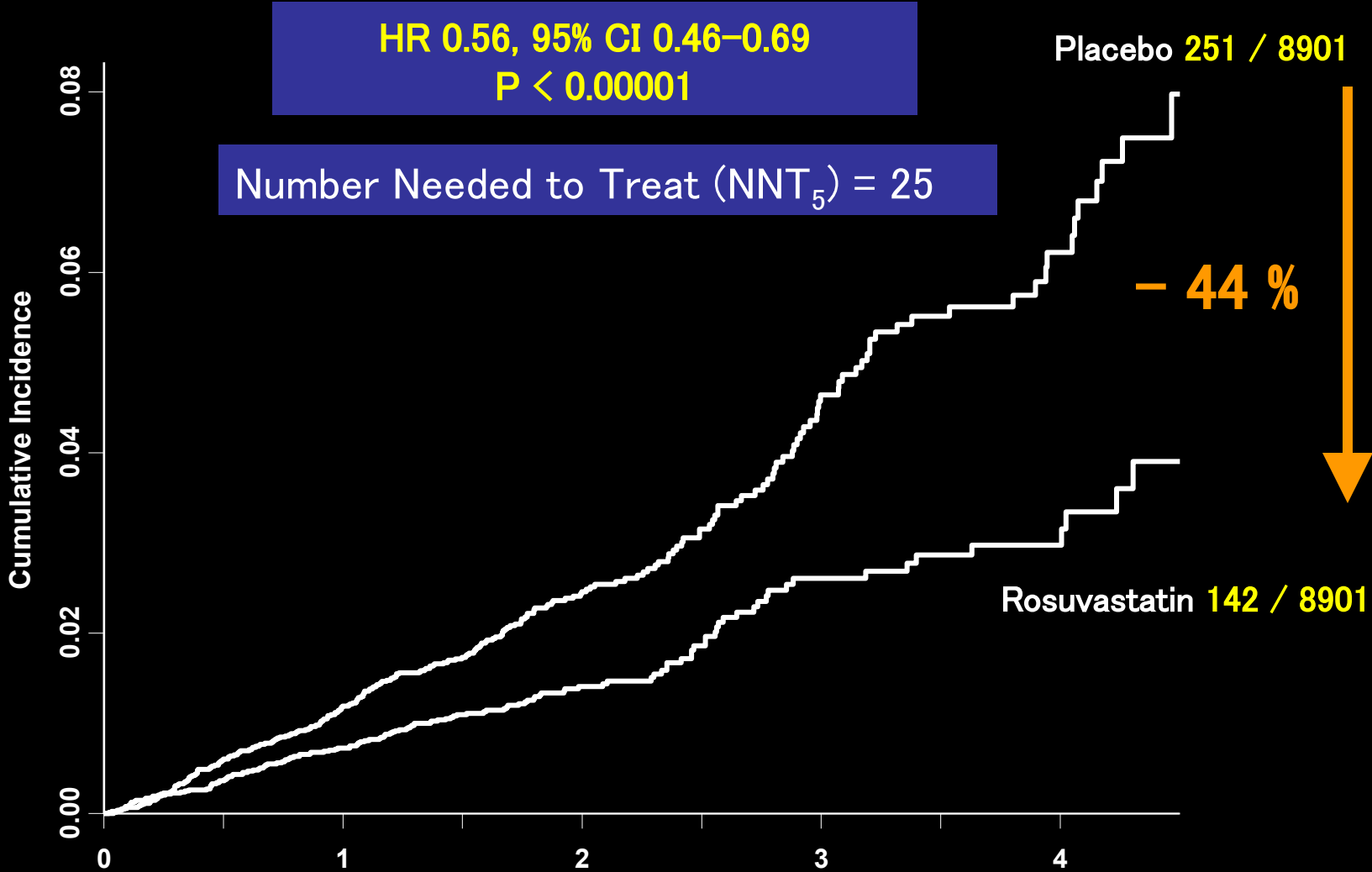
### IMPROVE-IT

Bohula et al, Circulation 2015;132:1224-33

# JUPITER

Ridker et al NEJM 2008;359:2195-2207

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



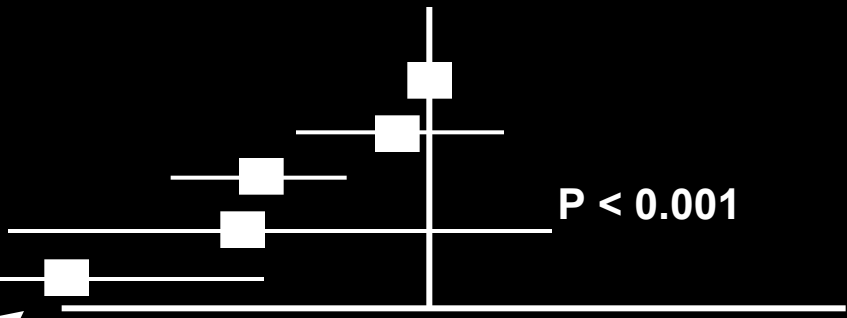
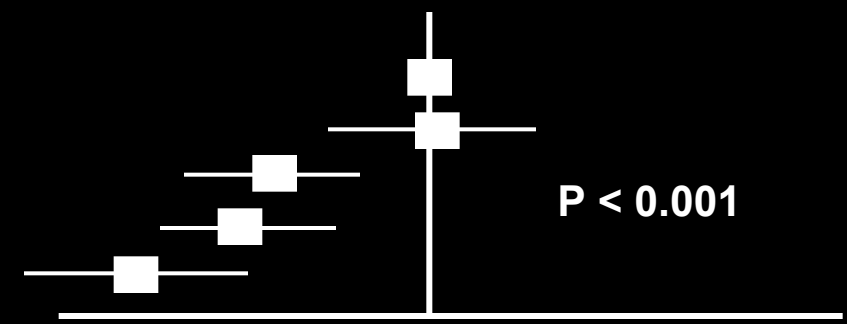
### Number at Risk

	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

LDL reduction, hsCRP reduction, or both?

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

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



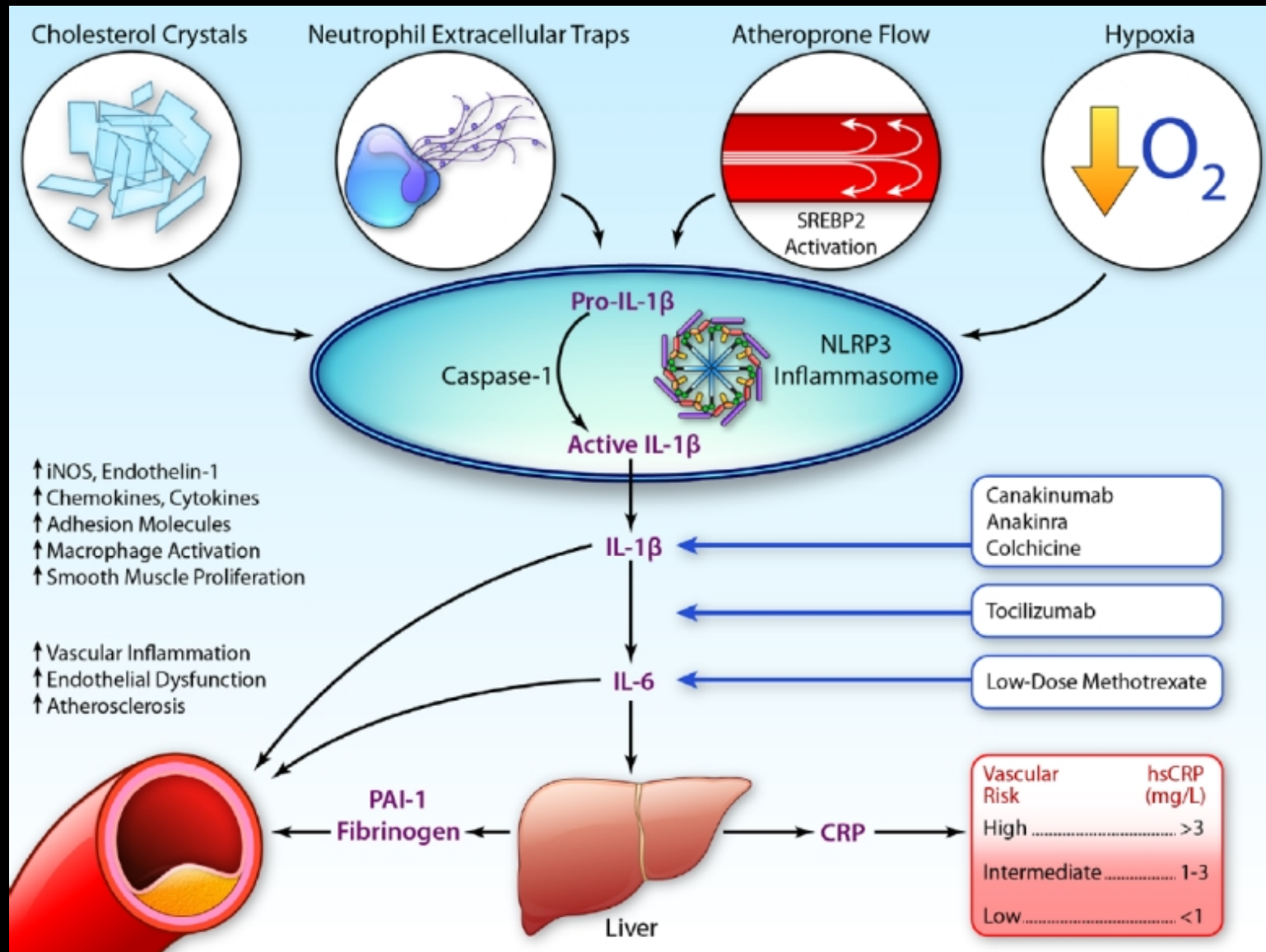
**Full Adjusted Hazard Ratio  
0.21, 95% CI 0.09-0.52, P < 0.0001**

0.25      0.5      1.0      2.0      4.0

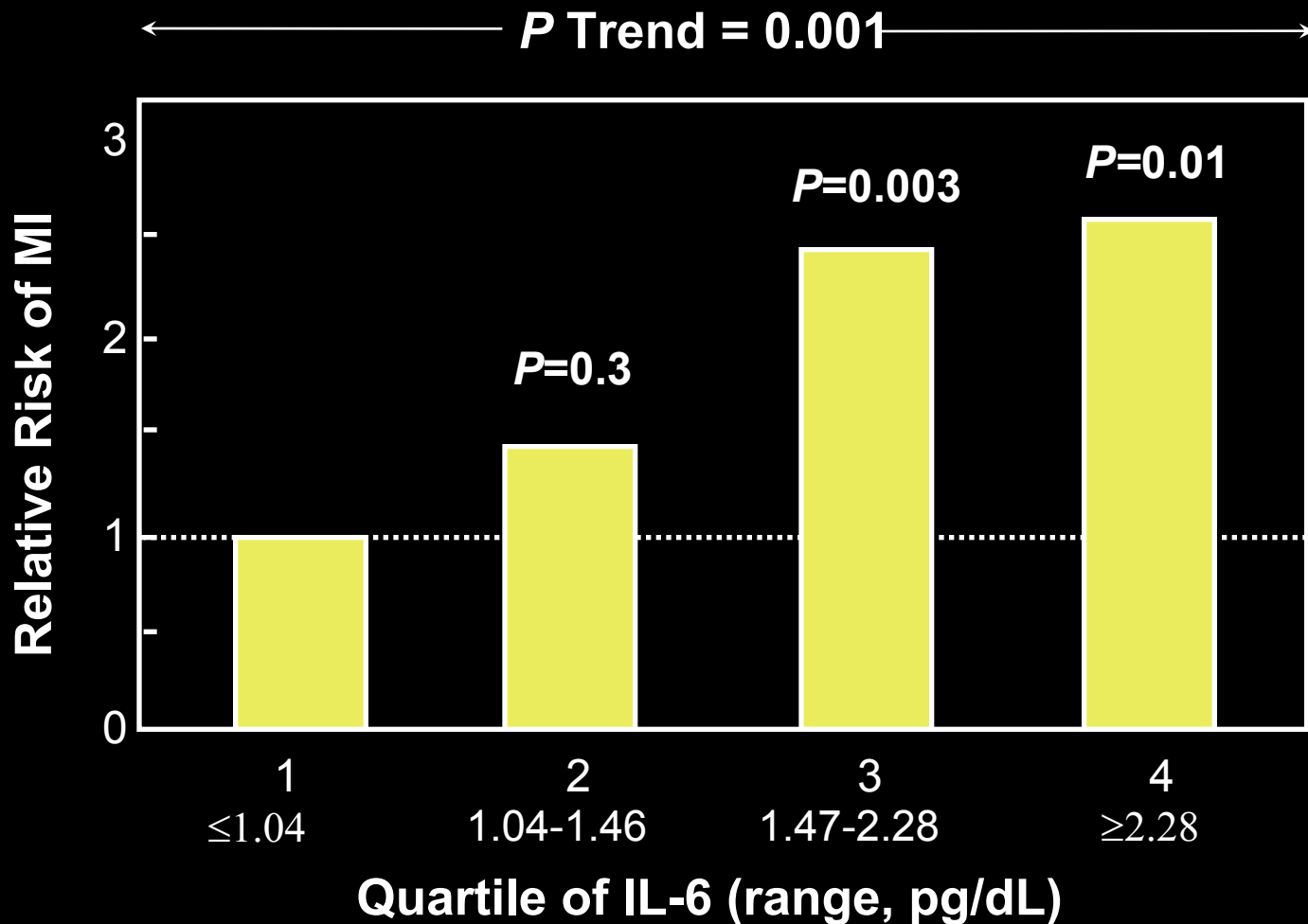
Rosuvastatin Better      Rosuvastatin Worse



# From CRP to IL-6 to IL-1: Moving Upstream to Identify novel Targets for Atheroprotection

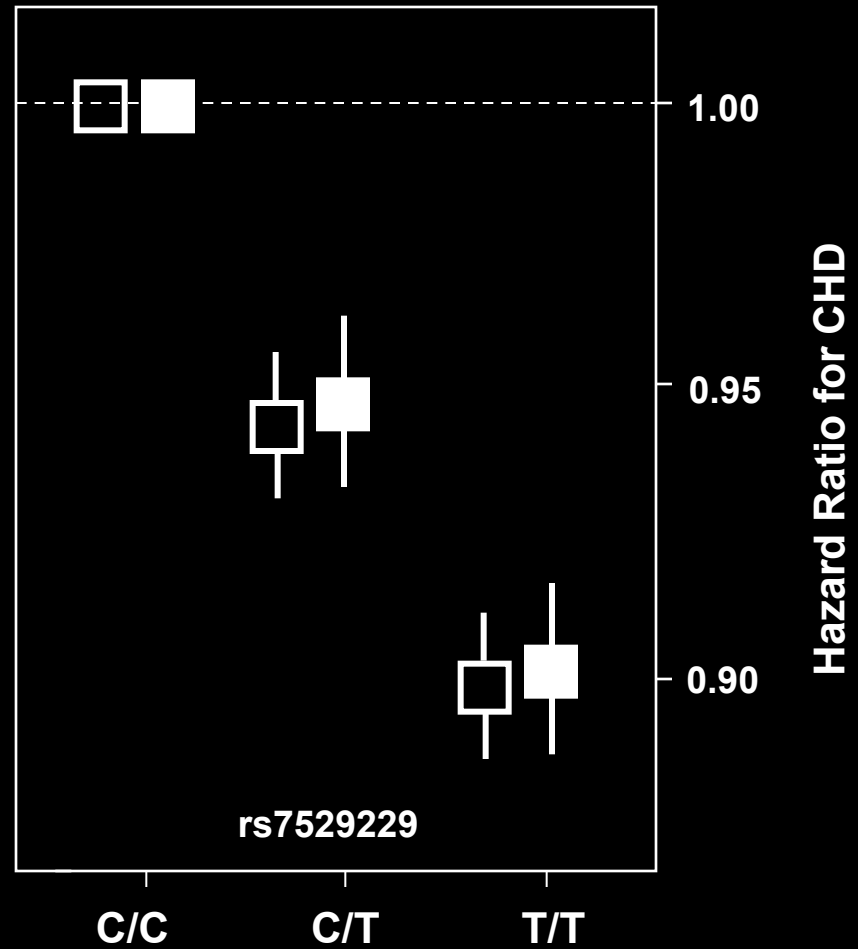
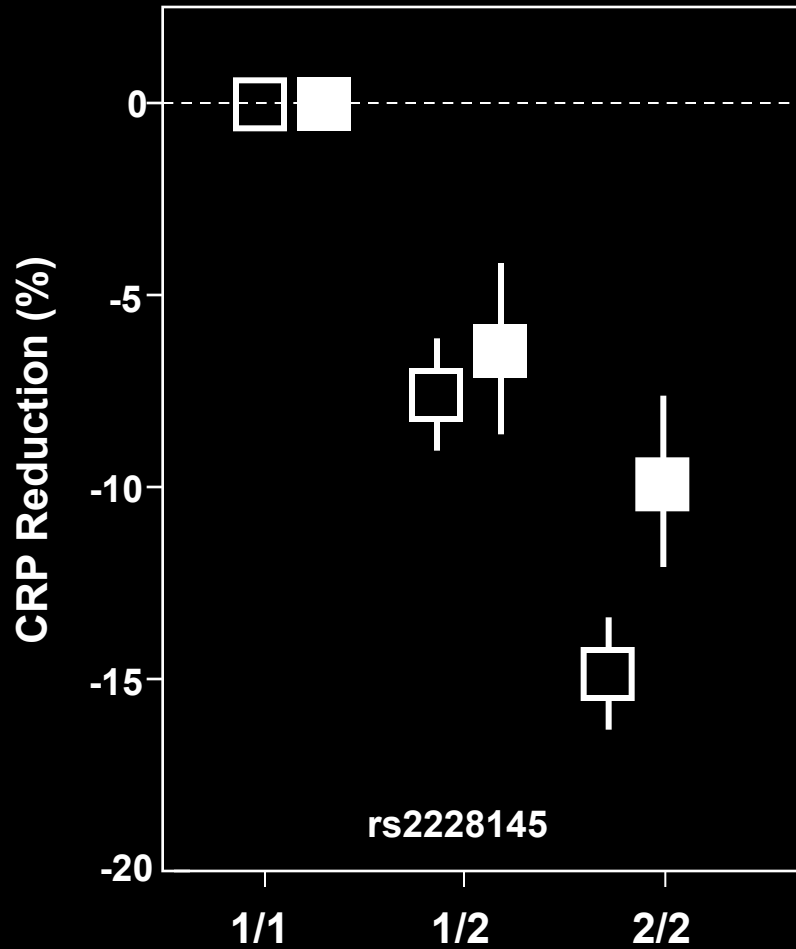


# IL-6 and Risk of Future MI in Apparently Healthy Men

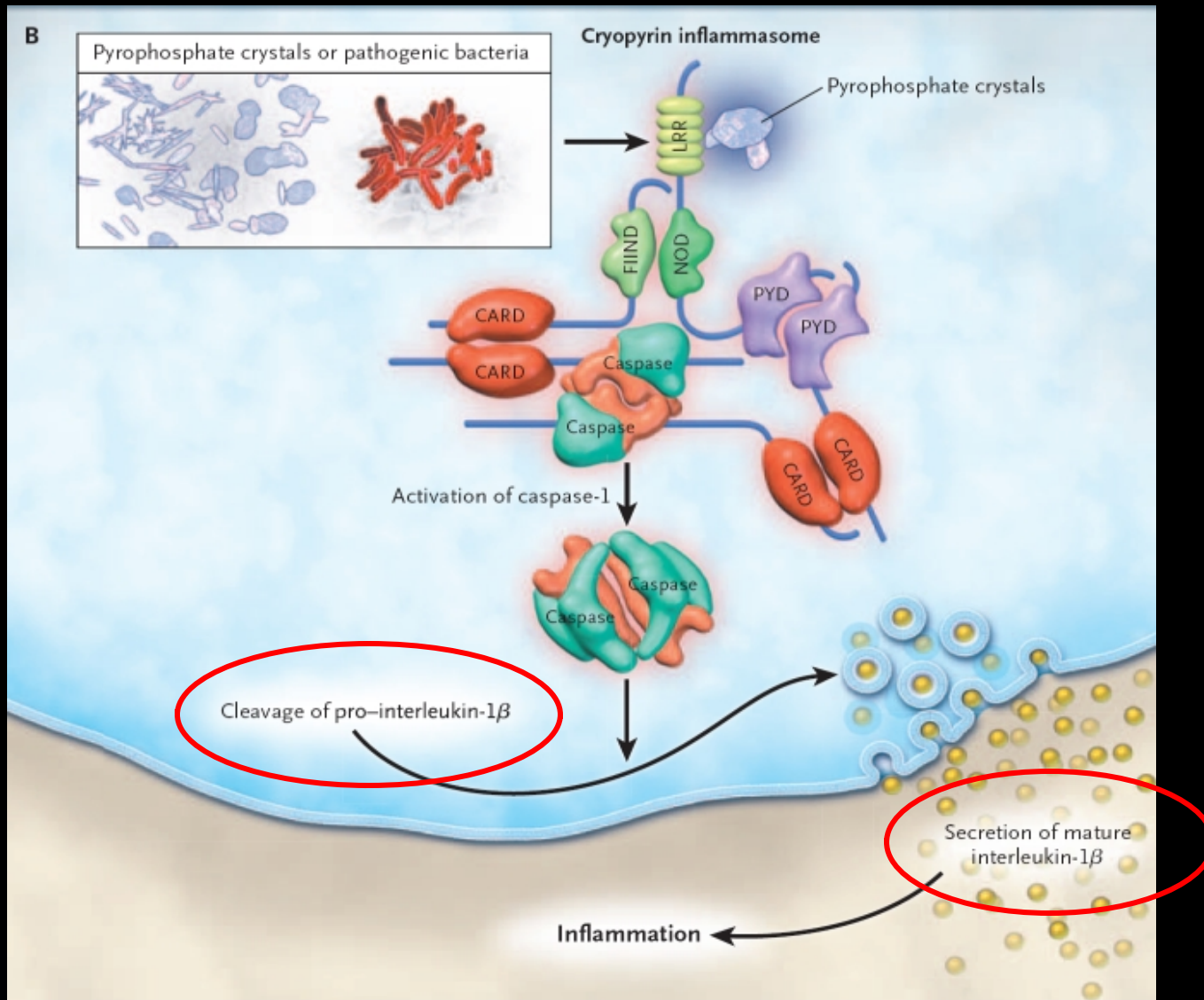


# Effects of Polymorphism in the IL-6 Receptor Signaling Pathway On Downstream CRP Levels and Risks of Coronary Heart Disease

CRP Reduction (%)  Hazard Ratio CHD 



# NLRP3 Cryopyrin Inflammasome, Caspase-1, and IL-1 $\beta$ Maturation Endogenous Danger Signals in Vascular Biology?



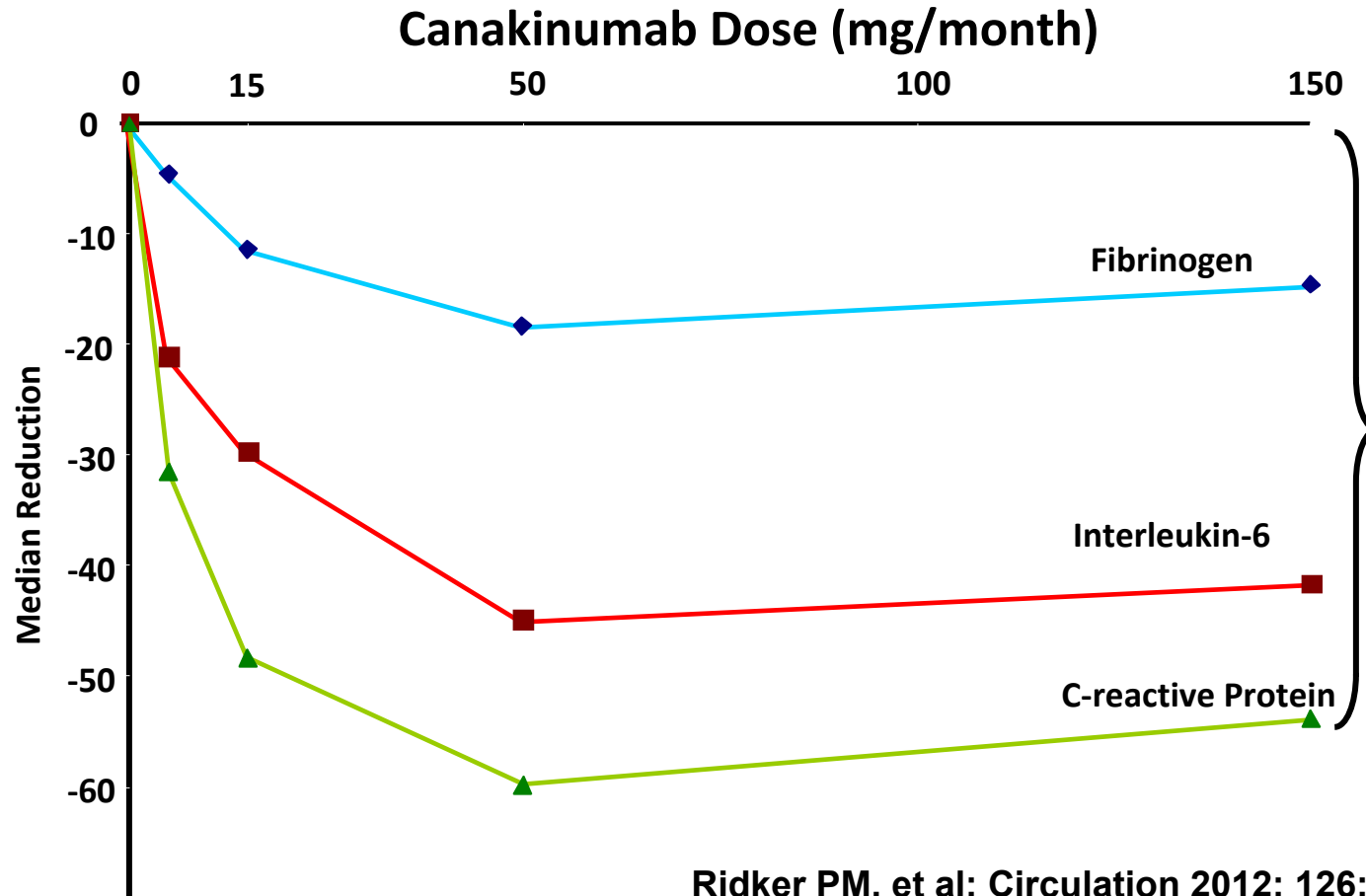
# Canakinumab (Novartis)

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- **high-affinity human monoclonal anti-human interleukin-1 $\beta$  (IL-1 $\beta$ ) antibody currently indicated for the treatment of IL-1 $\beta$  driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)**
- **designed to bind to human IL-1 $\beta$  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-1 $\beta$ Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial

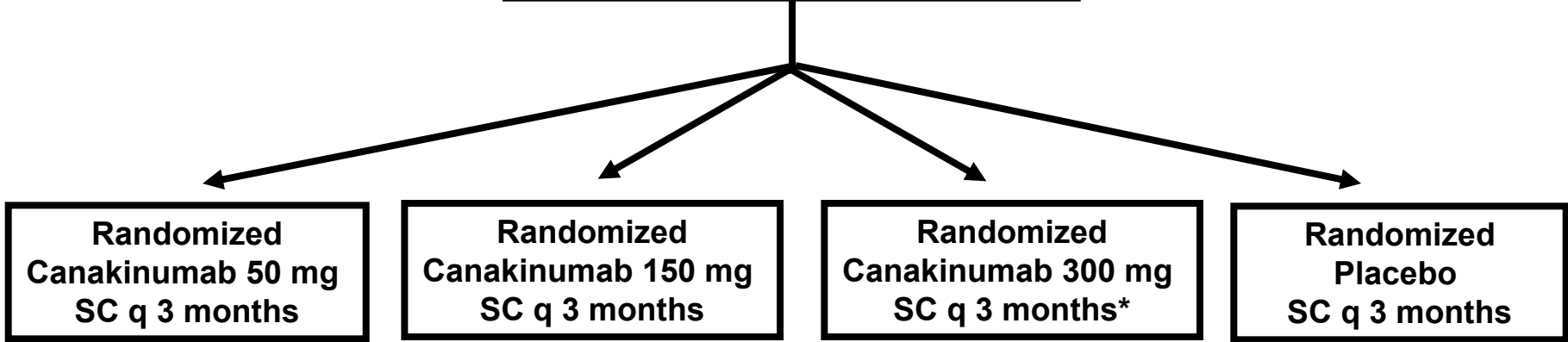


# Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)



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

N = 10,061  
39 Countries  
April 2011 - June 2017  
1490 Primary Events



**Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)**

**Key Secondary CV Endpoint: MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+)**

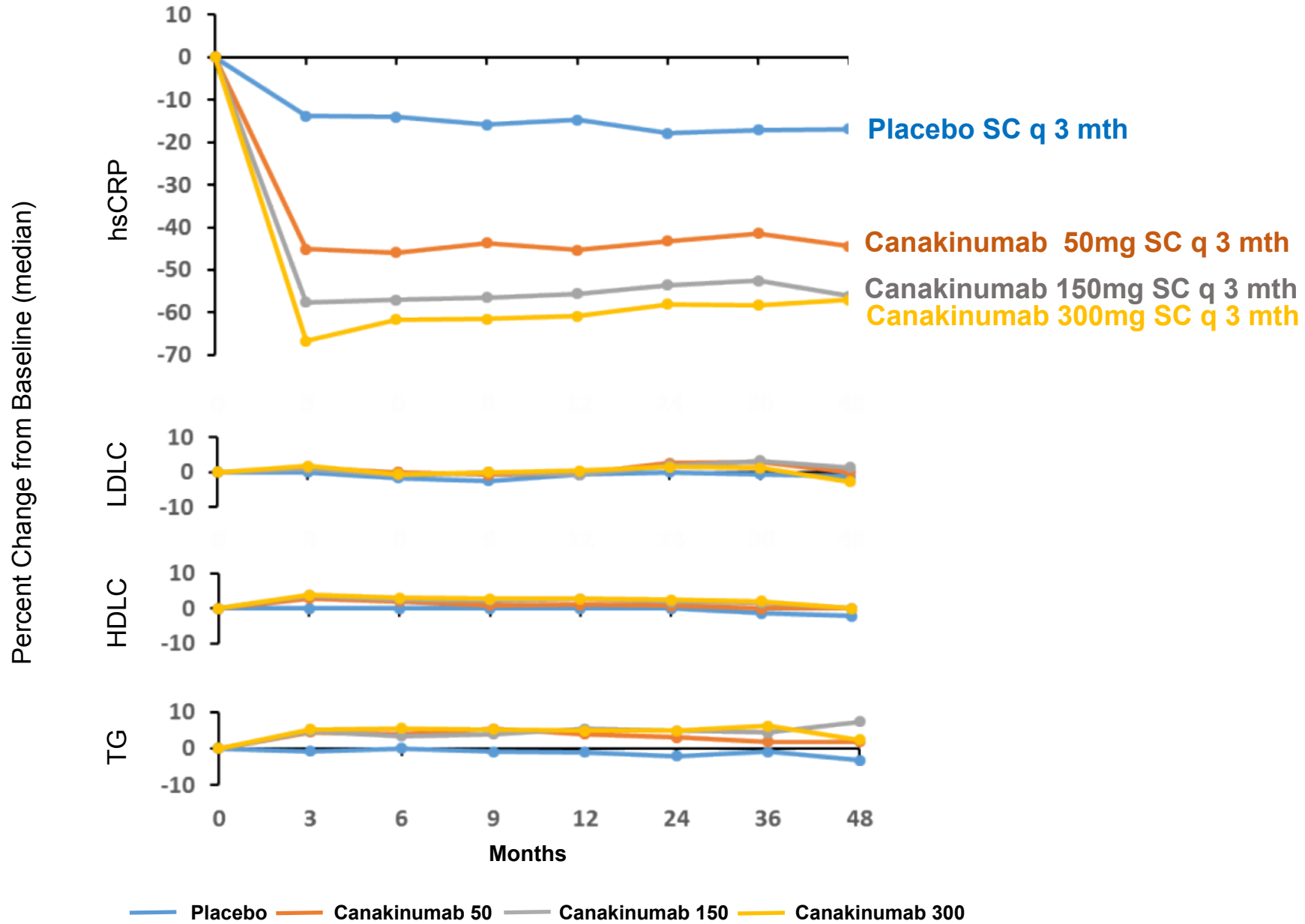
**Critical Non-Cardiovascular Safety Endpoints: Cancer and Cancer Mortality, Infection and Infection Mortality**

## CANTOS - Baseline Clinical Characteristics

Characteristic	Placebo (N=3347)	Canakinumab SC q 3 months		
		50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)
Age (years)	61.1	61.1	61.2	61.1
Female (%)	25.9	24.9	25.2	26.8
Current smoker (%)	22.9	24.5	23.4	23.7
Diabetes (%)	39.9	39.4	41.8	39.2
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6
Prior Revascularization (%)	79.6	80.9	82.2	80.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0
Triglycerides (mg/dL)	139	139	139	138
hsCRP (mg/L)	4.1	4.1	4.2	4.1



# CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)



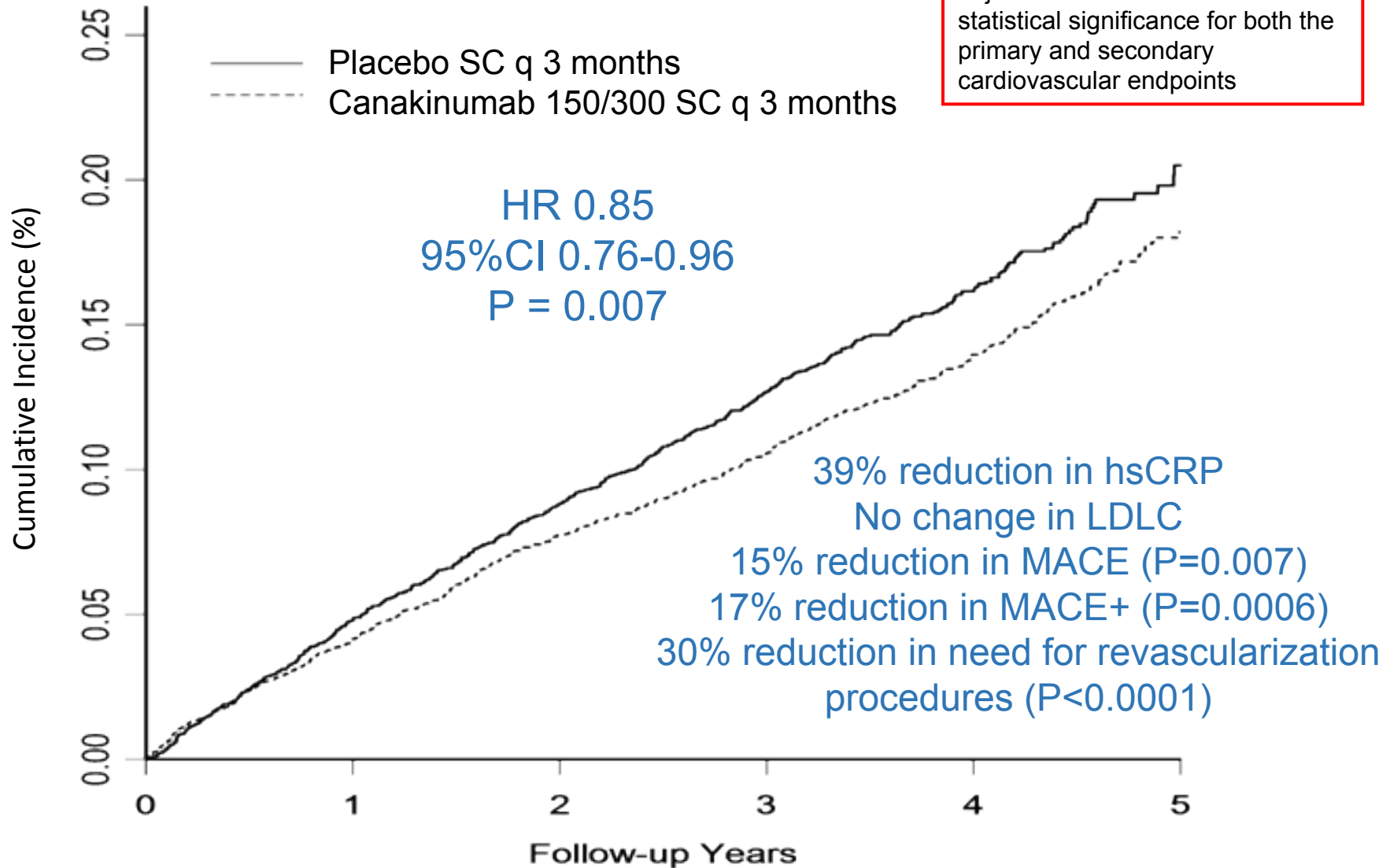
## CANTOS: Primary Clinical Outcome Effects on MACE and MACE +

		Canakinumab SC q 3 months			
	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
<b>Primary Endpoint</b>					
IR (per 100 person years)	4.5	4.1	3.9	3.9	0.020
HR	1.0	0.93	0.85	0.86	
95%CI	(referent)	0.80-1.07	0.74-0.98	0.75-0.99	
P	(referent)	0.30	0.021*	0.031	
<b>Secondary Endpoint</b>					
IR (per 100 person years)	5.1	4.6	4.3	4.3	0.003
HR	1.00	0.90	0.83	0.83	
95%CI	(referent)	0.78-1.03	0.73-0.95	0.72-0.94	
P	(referent)	0.11	0.005*	0.004	

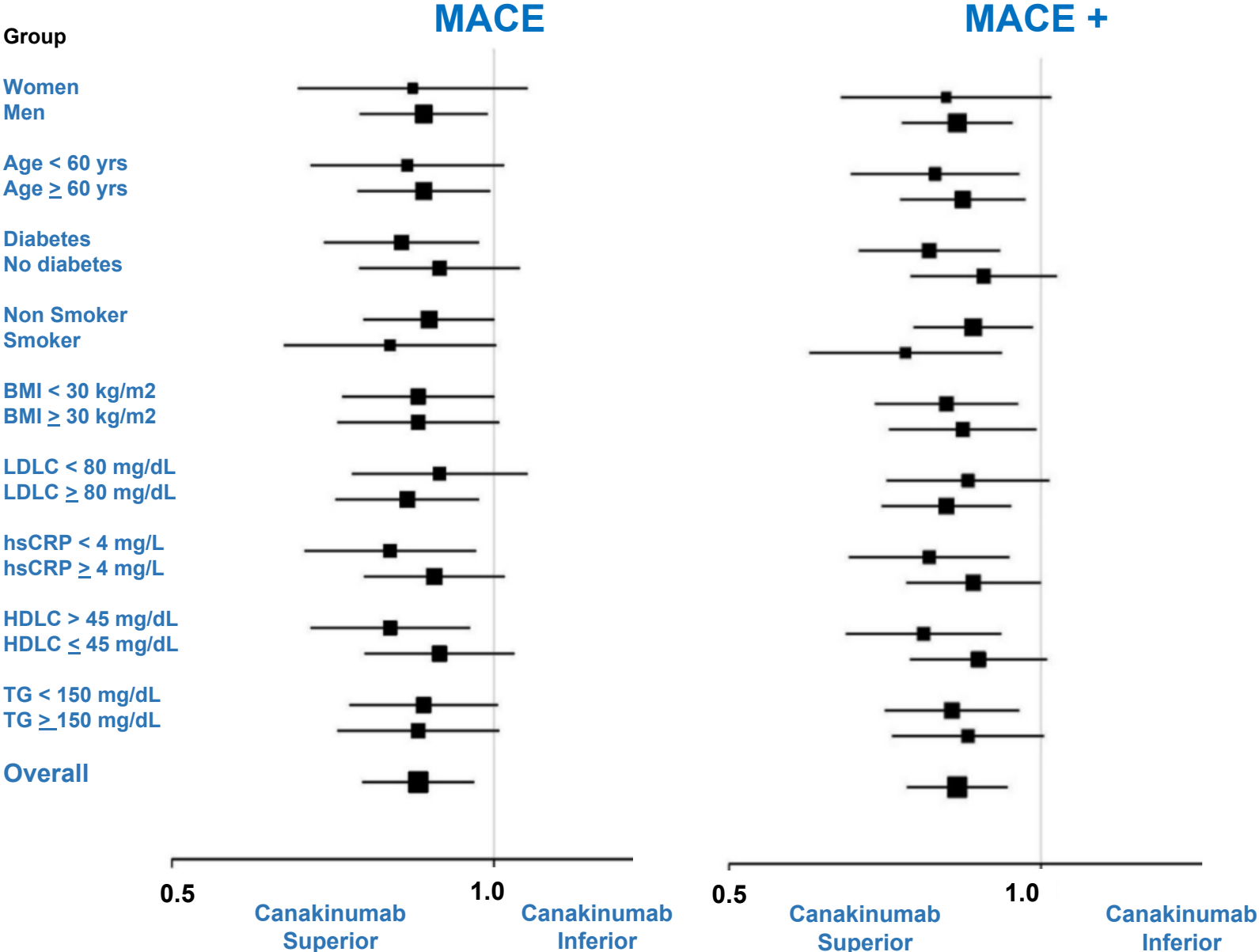
\*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures

# CANTOS: Primary Cardiovascular Endpoint (MACE)

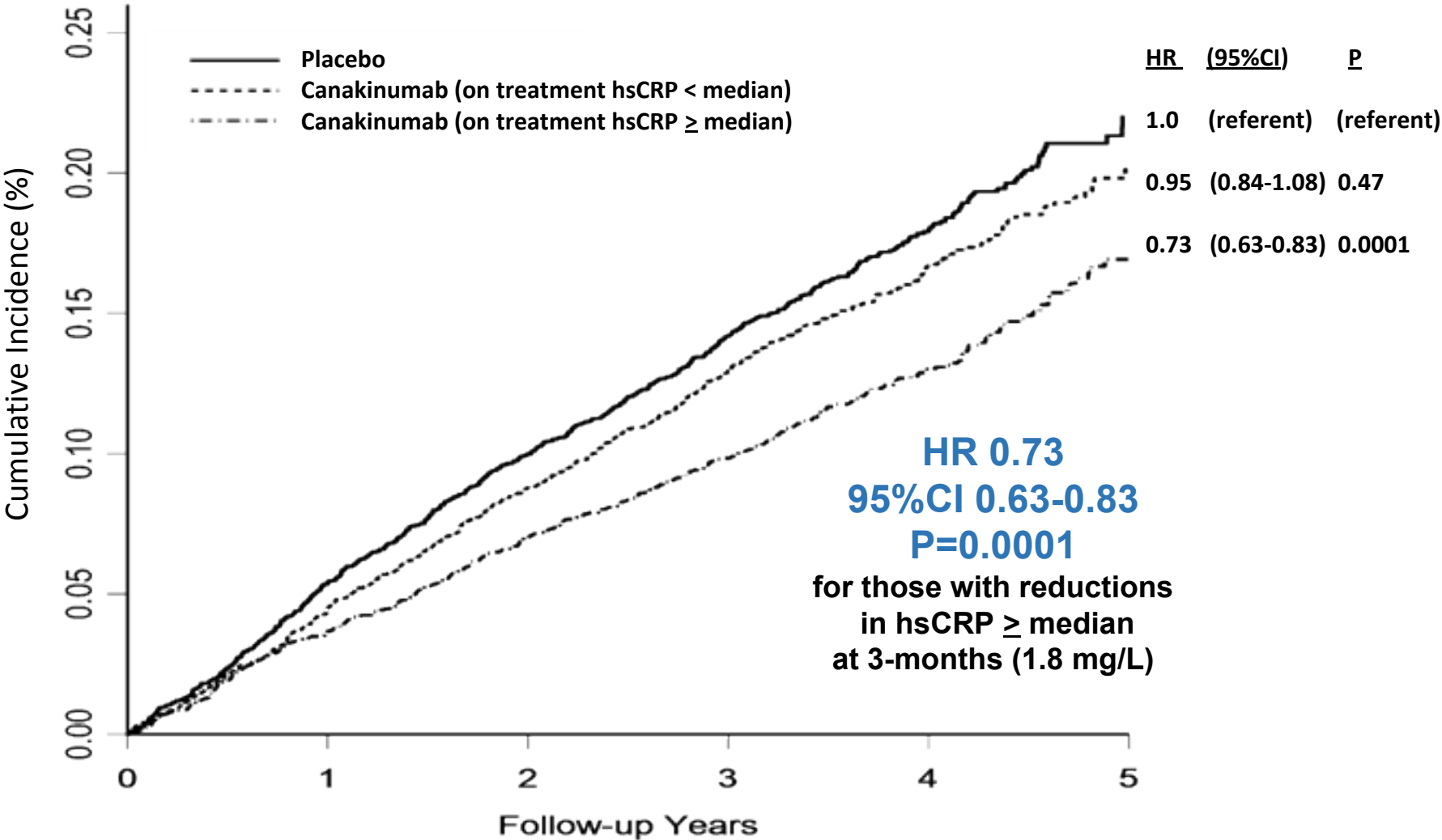
The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



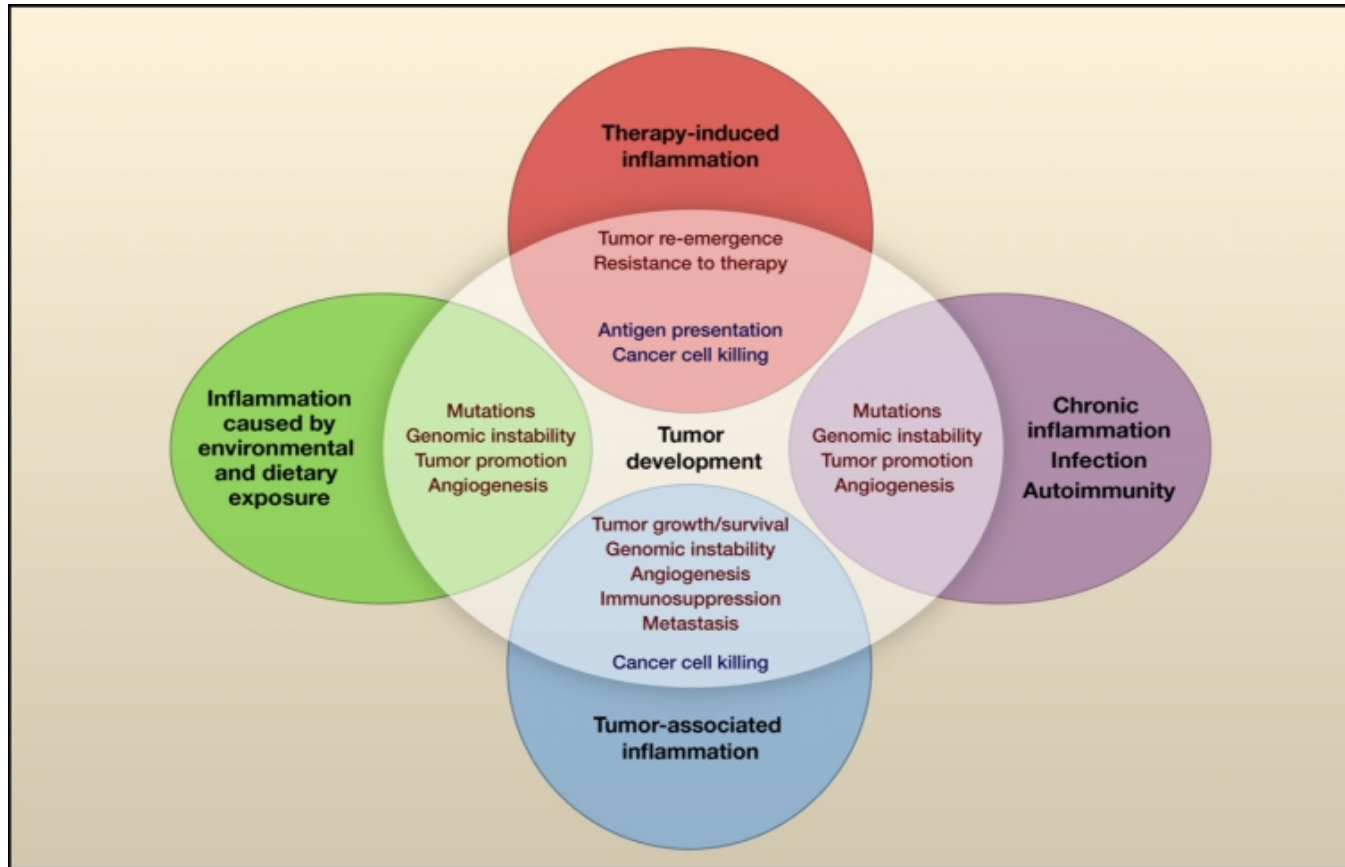
# CANTOS: Consistency of Effect Across All Patient Groups



# CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)



# Immunity, Inflammation, and Cancer



**Sub-clinical chronic inflammation increases cancer risk (hsCRP is also a risk factor for certain cancers, in particular lung cancer)**

**Inflammation in the tumor micro-environment impacts upon tumor initiation, progression, invasiveness, and metastatic progression**

**Grivennikov, Greten, Karin. Cell 2010;140:883-99.**

# Chronic Inflammation, Tumor Progression, and IL-1 Inhibition

Cancer Metastasis Rev (2006) 25:387–408  
DOI 10.1007/s10555-006-9004-4

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## **The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions**

Ron N. Apte · Shahar Dotan · Moshe Elkabets ·  
Malka R. White · Eli Reich · Yaron Carmi ·  
Xiaping Song · Tatyana Dvozkin · Yakov Krelin ·  
Elena Voronov

**Ron Apte, et al;  
Cancer Metastasis Rev.  
2006;25:387-408.**

**Anne Lewis, et al;  
J Transl Med.  
2006;4:48.**

## **Journal of Translational Medicine**

Review

**Open Access**

### **Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment**

Anne M Lewis<sup>1,2</sup>, Sheelu Varghese<sup>1,3</sup>, Hui Xu<sup>1</sup> and H Richard Alexander\*<sup>1,3</sup>

Cancer Metastasis Rev (2010) 29:317–329  
DOI 10.1007/s10555-010-9229-0

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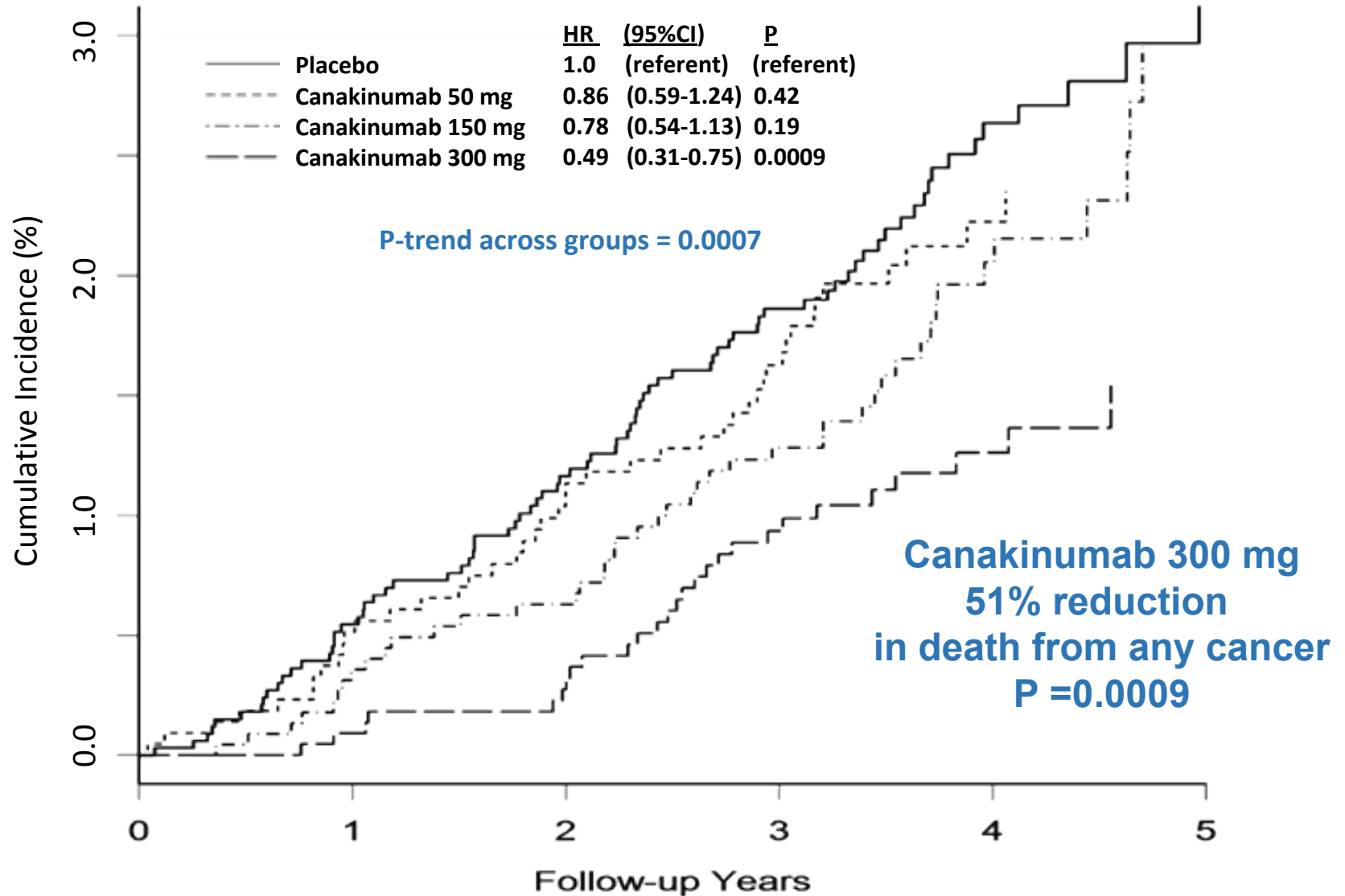
## **Why not treat human cancer with interleukin-1 blockade?**

Charles A. Dinarello

**Charles A. Dinarello.  
Cancer Metastasis  
Rev  
2010;29:317-329.**

# CANTOS: Additional Non-Cardiovascular Clinical Benefits

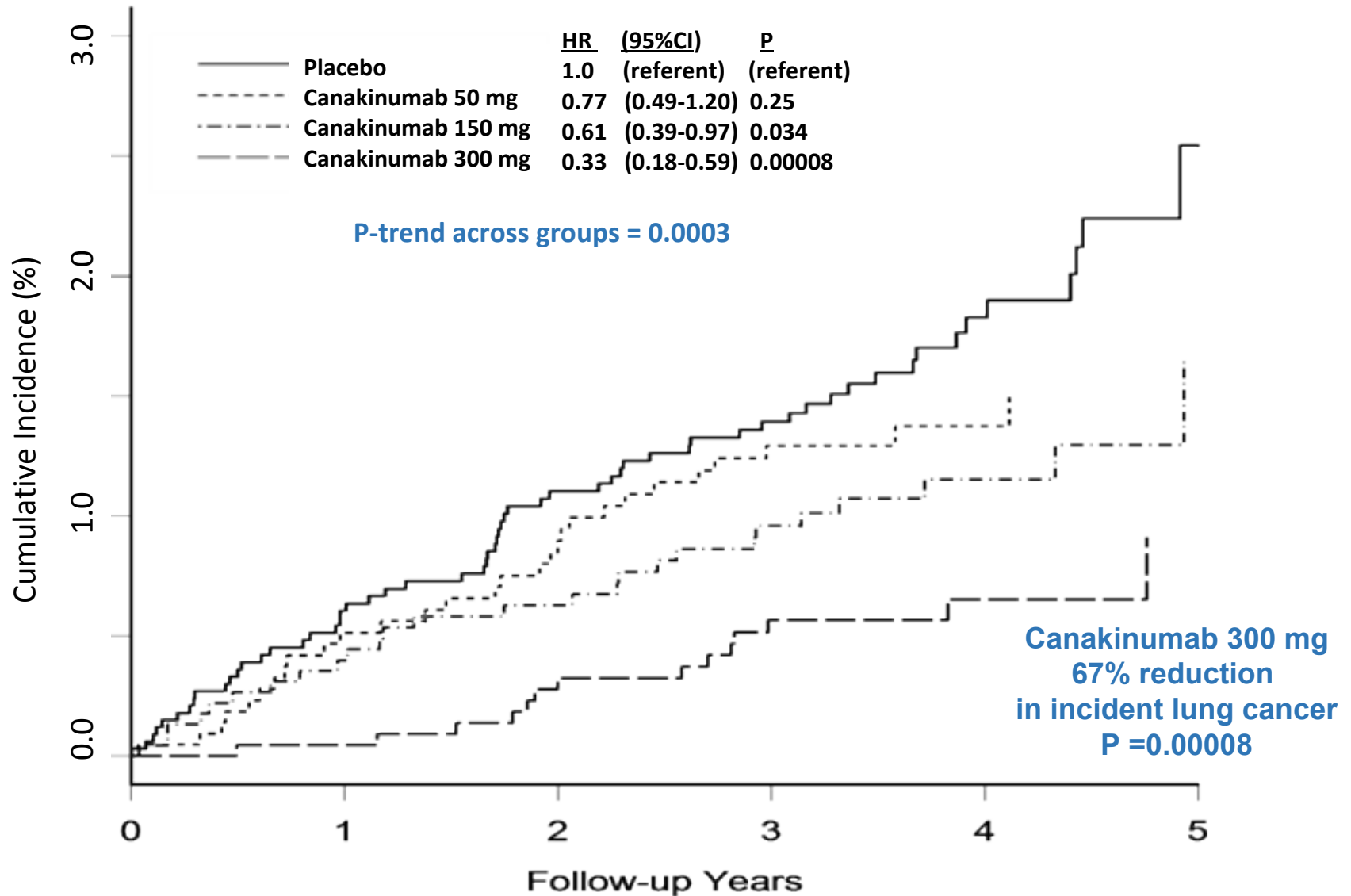
## Cancer Mortality





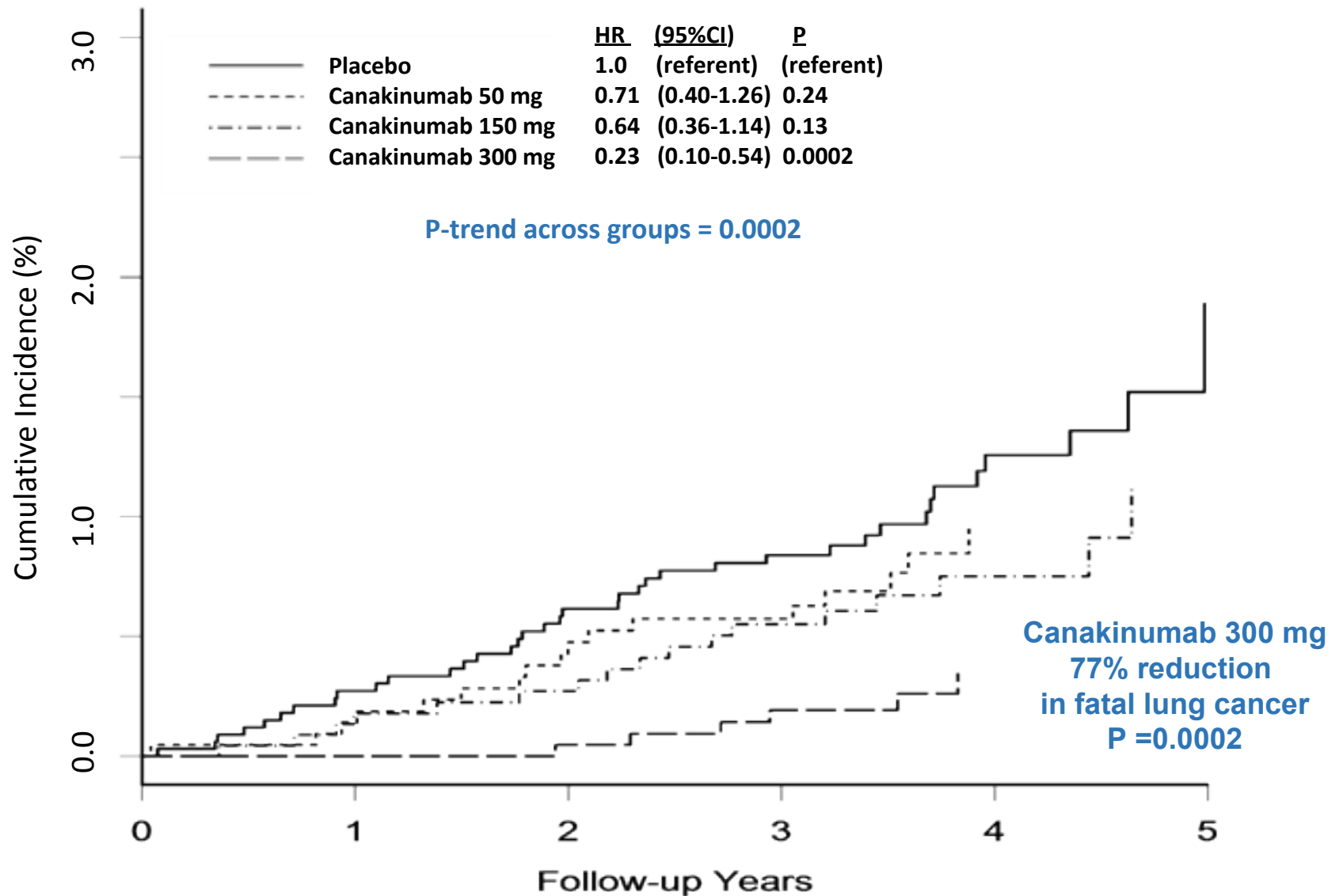
# CANTOS: Additional Non-Cardiovascular Clinical Benefits

## Incident Lung Cancer



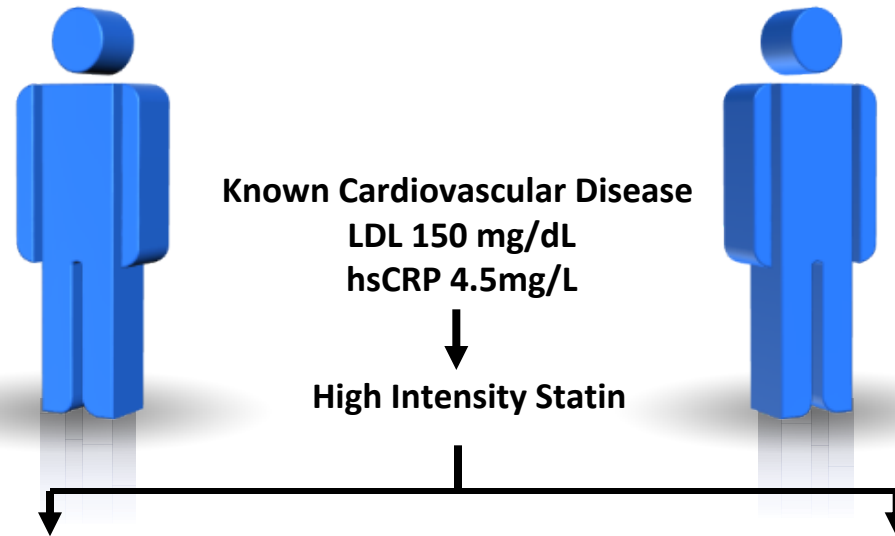
# CANTOS: Additional Non-Cardiovascular Clinical Benefits

## Fatal Lung Cancer



# Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. *Eur Heart J* 2016;37:1720-22



## “Residual Cholesterol Risk”

LDL 110 mg/dL  
hsCRP 1.8 mg/L



Additional  
LDL Reduction

**IMPROVE-IT : Ezetimibe 6% RRR**  
**FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR**

## “Residual Inflammatory Risk”

LDL 80 mg/dL  
hsCRP 3.8 mg/L

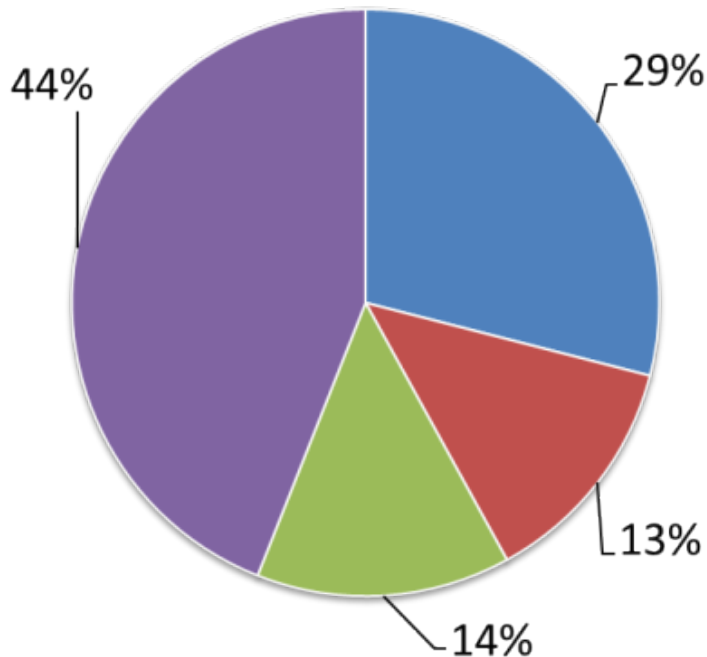


Additional  
Inflammation Reduction

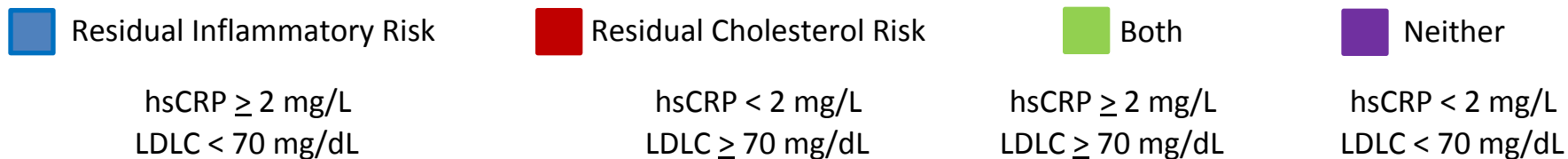
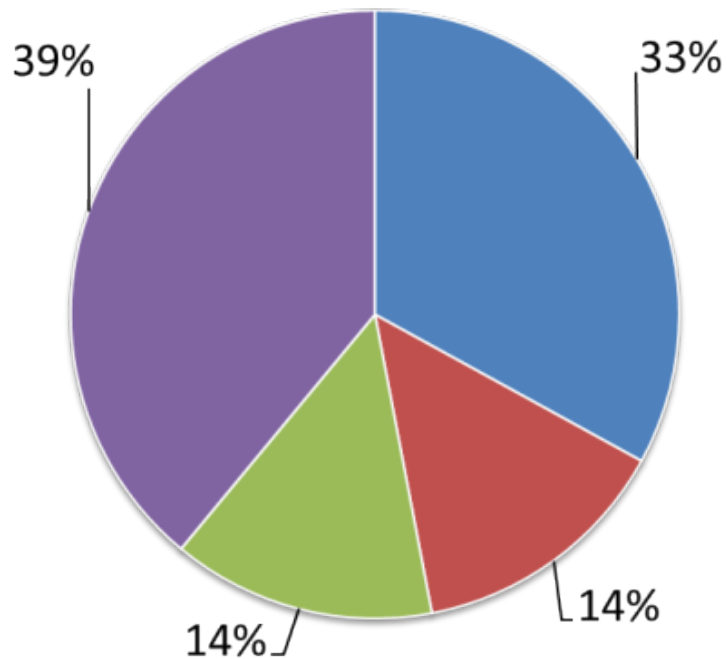
**No Prior Proof of Concept**  
**Canakinumab 150mg SC q 3 months 15%RRR**

# How Common is Residual Inflammatory Risk?

## PROVE-IT



## IMPROVE-IT



# Inflammation, Atherothrombosis, and Vascular Prevention: Three Translational Questions

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Is there evidence that individuals with elevated levels of inflammatory biomarkers are at high vascular risk even when other risk factors are acceptable? **Yes (hsCRP, 1997)**

Is there evidence that individuals identified at increased risk due to inflammation benefit from a therapy they otherwise would not have received? **Yes (statins, JUPITER 2008)**

Is there evidence that reducing inflammation per se will reduce vascular events? **Yes (CANTOS, ESC 2017)**

**“Lower is better” appears to be true for both LDLC and hsCRP in both primary and secondary prevention**

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# CANTOS : Adding a New Axis to the Oxford LDL Lowering Line

