

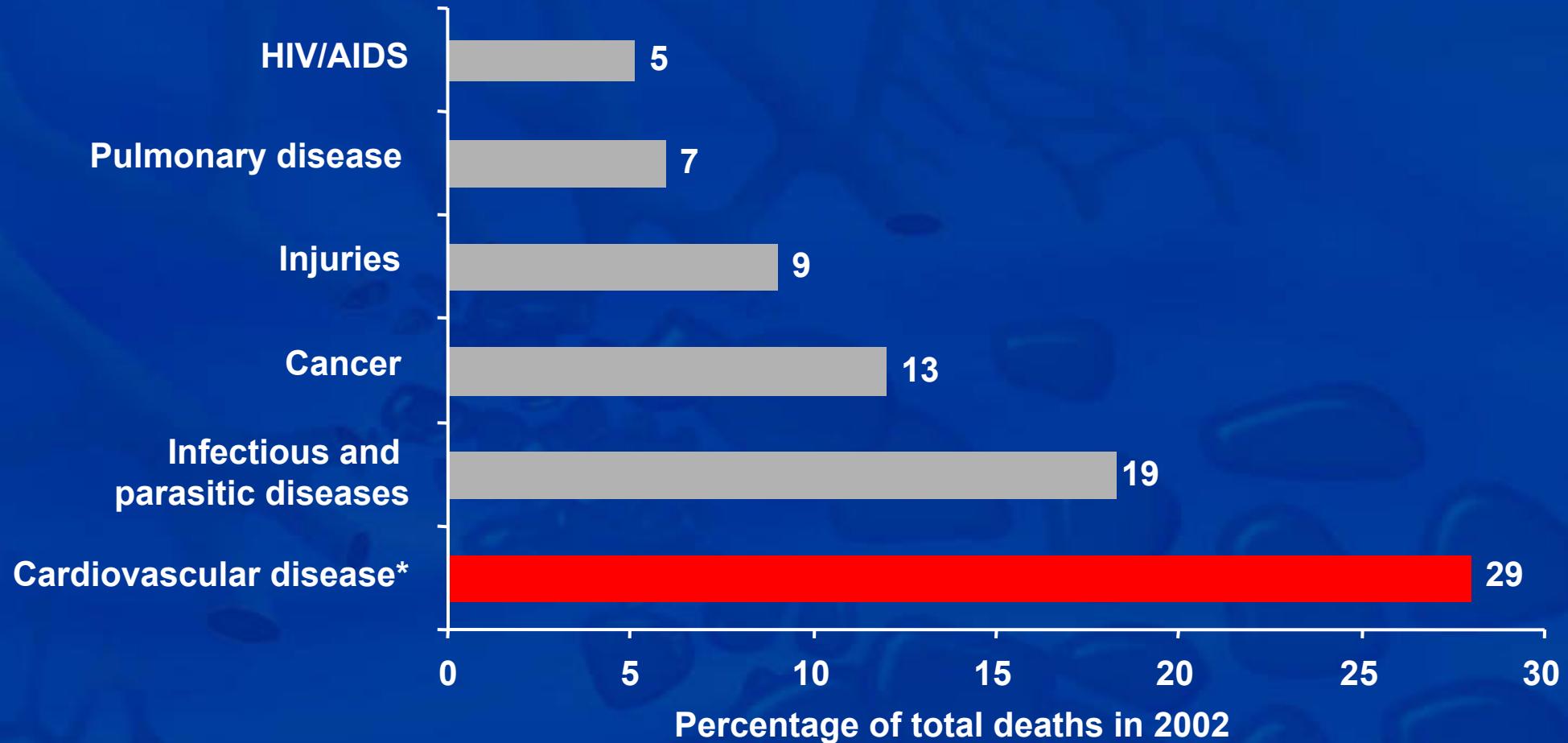


**hsCRP: ΑΠΟΤΕΛΕΙ ΘΕΡΑΠΕΥΤΙΚΟ ΣΤΟΧΟ  
ΣΤΗΝ ΠΡΟΛΗΨΗ ΤΩΝ ΚΑΡΔΙΑΓΓΕΙΑΚΩΝ  
ΕΠΕΙΣΟΔΙΩΝ:-ΥΠΕΡ**

**Ευάγγελος Λυμπερόπουλος**

**Λέκτορας Παθολογίας Ιατρικής Σχολής Παν/μίου Ιωαννίνων**

# Cardiovascular Disease is the Leading Cause of Death Worldwide<sup>1</sup>



\*Ischemic heart disease, cerebrovascular disease, hypertensive heart disease, inflammatory heart disease and rheumatic heart disease

# ΑΝΕΞΑΡΤΗΤΑ ΑΠΟ ΤΑ ΕΠΙΠΠΕΔΑ ΤΩΝ ΛΙΠΙΔΙΩΝ

ΒΑΣΙΚΟΣ ΣΤΟΧΟΣ ΤΗΣ ΑΓΩΓΗΣ:

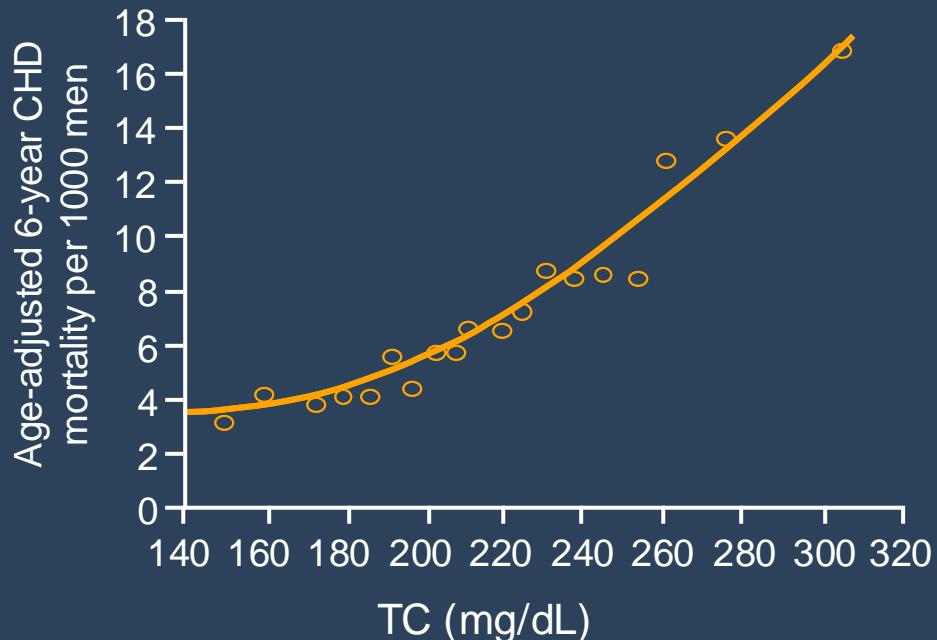
Η ΜΕΙΩΣΗ ΤΗΣ LDL CHOL

# Η LDL CHOL ΩΣ ΒΑΣΙΚΟΣ ΣΤΟΧΟΣ ΤΗΣ ΥΠΟΛΙΤΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ

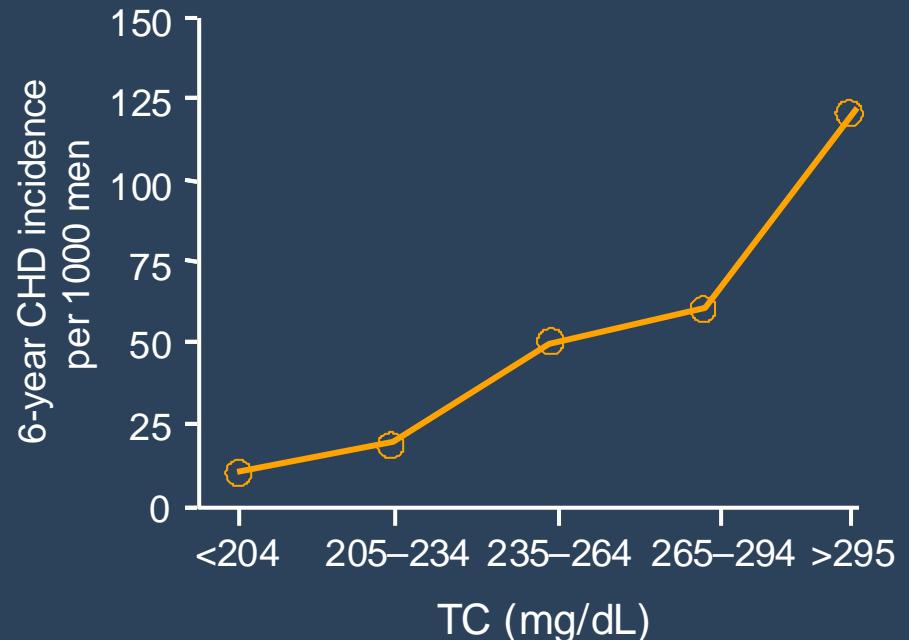
- ❑ Η αύξηση της LDL CHOL είναι ανεξάρτητος παράγοντας κινδύνου
- ❑ Οι LDL είναι αθηρωγόνα σωματίδια
- ❑ Η μείωση της LDL CHOL → σημαντική μείωση των συμβαμάτων

# *Epidemiologic Data Demonstrated a Strong Causal Link Between Elevated TC and CHD*

**Multiple Risk Factor Intervention Trial (MRFIT) N=361,662**



**Framingham Heart Study (FHS) N=5209**



TC=total cholesterol; CHD=coronary heart disease.

Martin MJ et al. *Lancet*. 1986;2:933-936; Castelli WP. *Am J Med*. 1984;76:4-12.

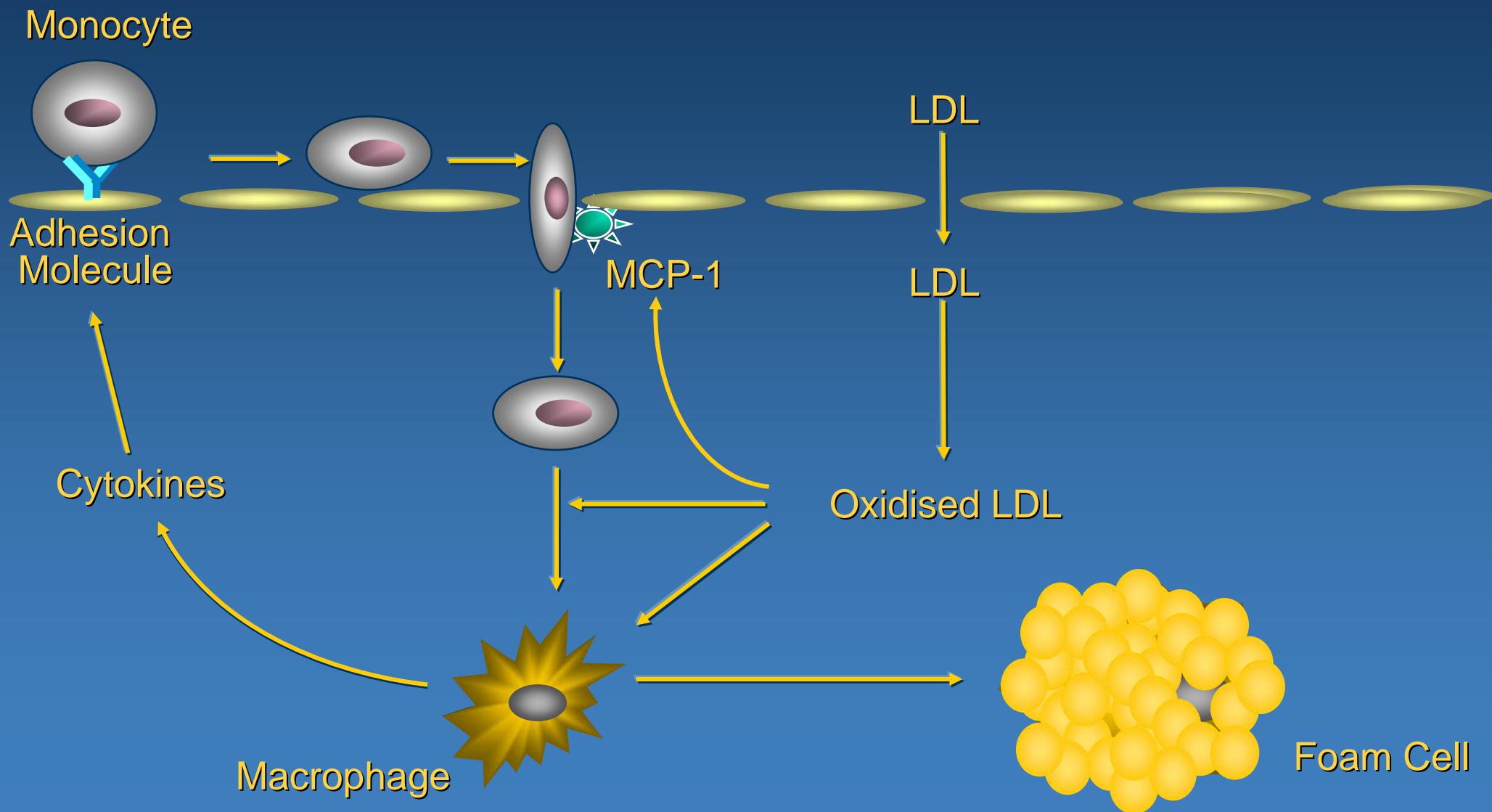
# Η LDL CHOL ΉΣ ΒΑΣΙΚΟΣ ΣΤΟΧΟΣ ΤΗΣ ΥΠΟΛΙΤΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ

□ Η αύξηση της LDL CHOL είναι ανεξάρτητος παράγοντας κινδύνου

□ Οι LDL είναι αθηρωγόνα σωματίδια

□ Η μείωση της LDL CHOL → σημαντική μείωση των συμβαμάτων

# ROLE OF LDL IN CAUSING ATHEROSCLEROSIS



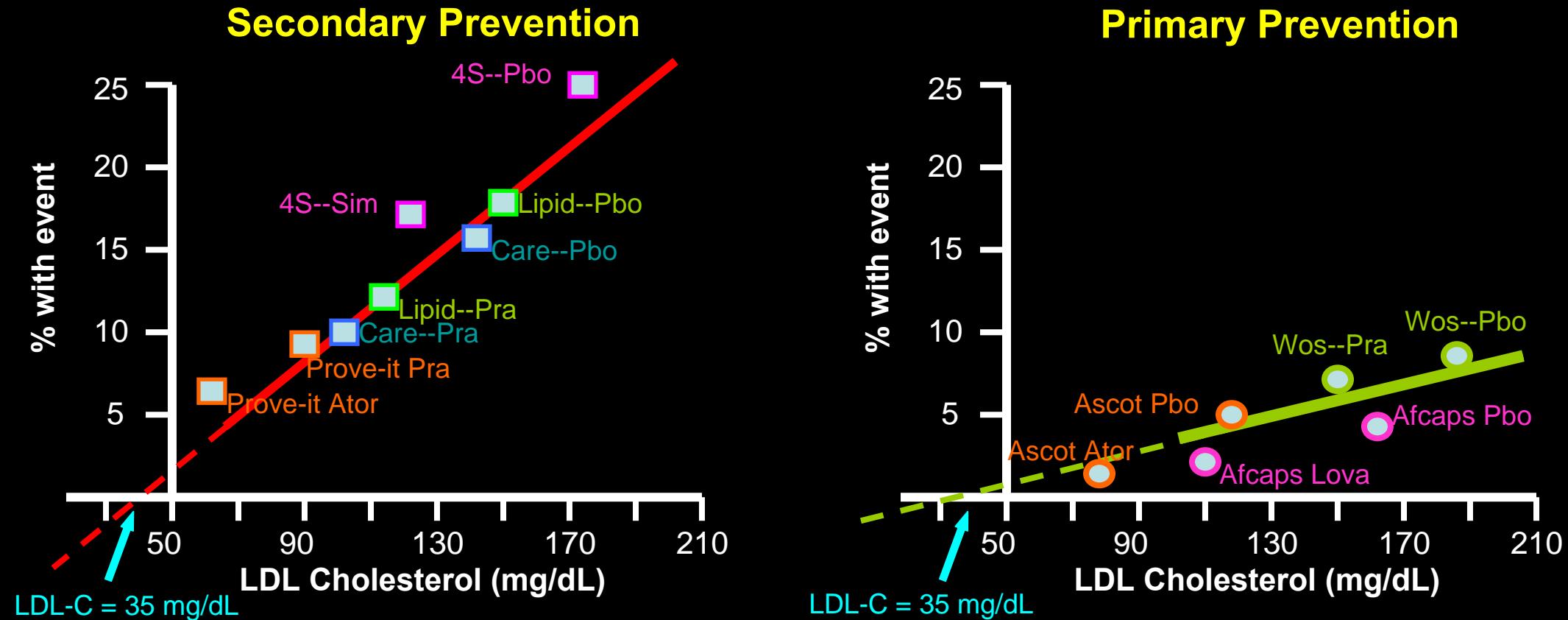
# Η LDL CHOL ΩΣ ΒΑΣΙΚΟΣ ΣΤΟΧΟΣ ΤΗΣ ΥΠΟΛΙΤΠΙΔΑΙΜΙΚΗΣ ΑΓΩΓΗΣ

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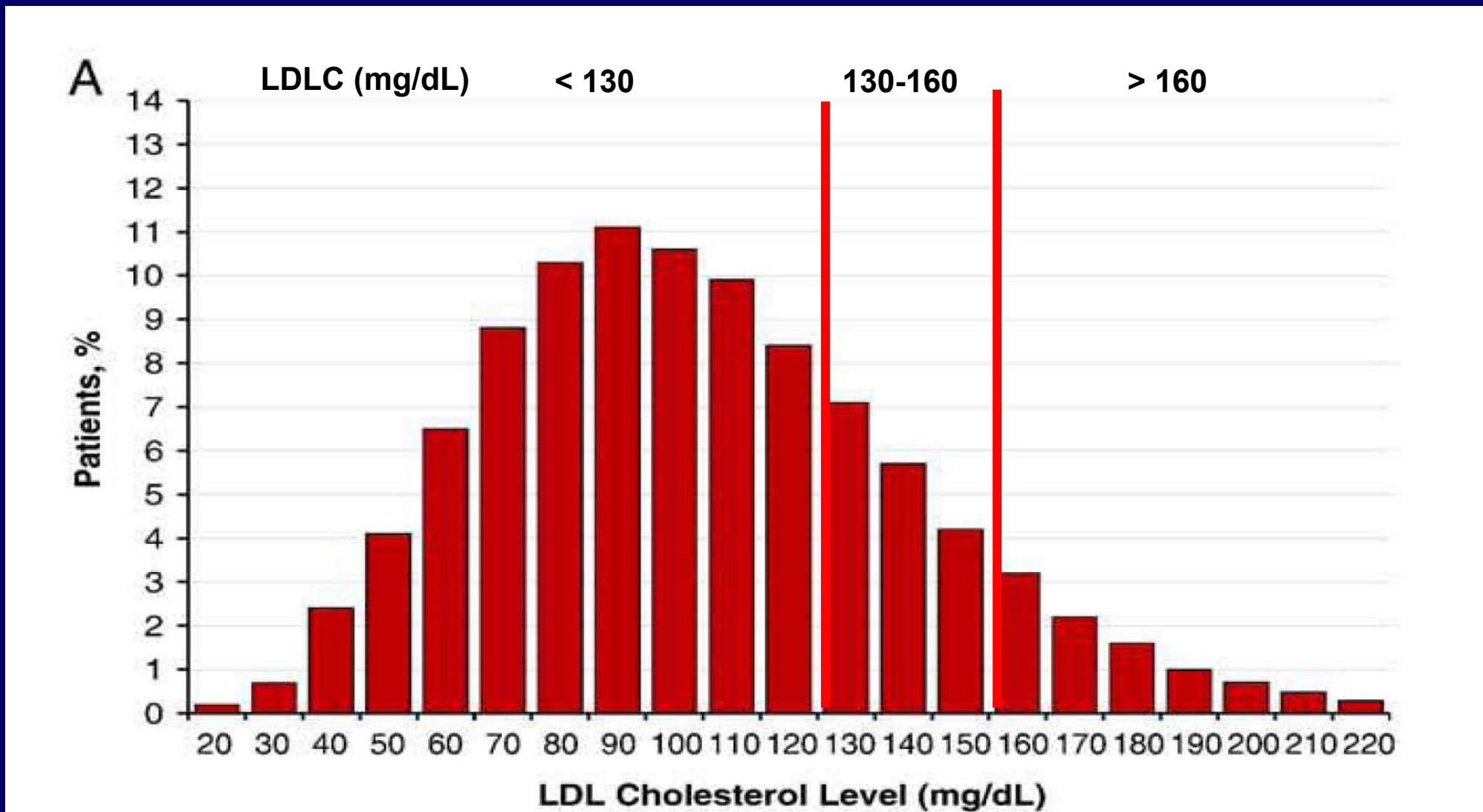
# LDL LOWERING AND EVENT REDUCTION: HOW LOW DO WE GO?



## Conclusions:

- 1) Absolute risk of subjects with disease is greater and absolute benefits of therapy higher.
- 2) Risk of an event in both groups approaches zero at LDL-C below 50 mg/dL.

# LDLC Levels in 136,905 Patients Hospitalized With CAD: 2000- 2006



# Υψηλής ευαισθησίας C-αντιδρώσα πρωτεΐνη (hsCRP)

Curr Vasc Pharmacol 2008;6:258-70

**ΣΤΟΧΟΣ ΤΗΣ ΑΓΩΓΗΣ:**

**Η ΜΕΙΩΣΗ ΤΗΣ hsCRP**

**???**

# Η hsCRP ΩΣ ΣΤΟΧΟΣ ΤΗΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΑΓΩΓΗΣ

❑ Η αύξηση της hsCRP είναι ανεξάρτητος παράγοντας κινδύνου??

❑ Η hsCRP προάγει την αθηρωμάτωση??

❑ Η μείωση της hsCRP → σημαντική μείωση των συμβαμάτων??

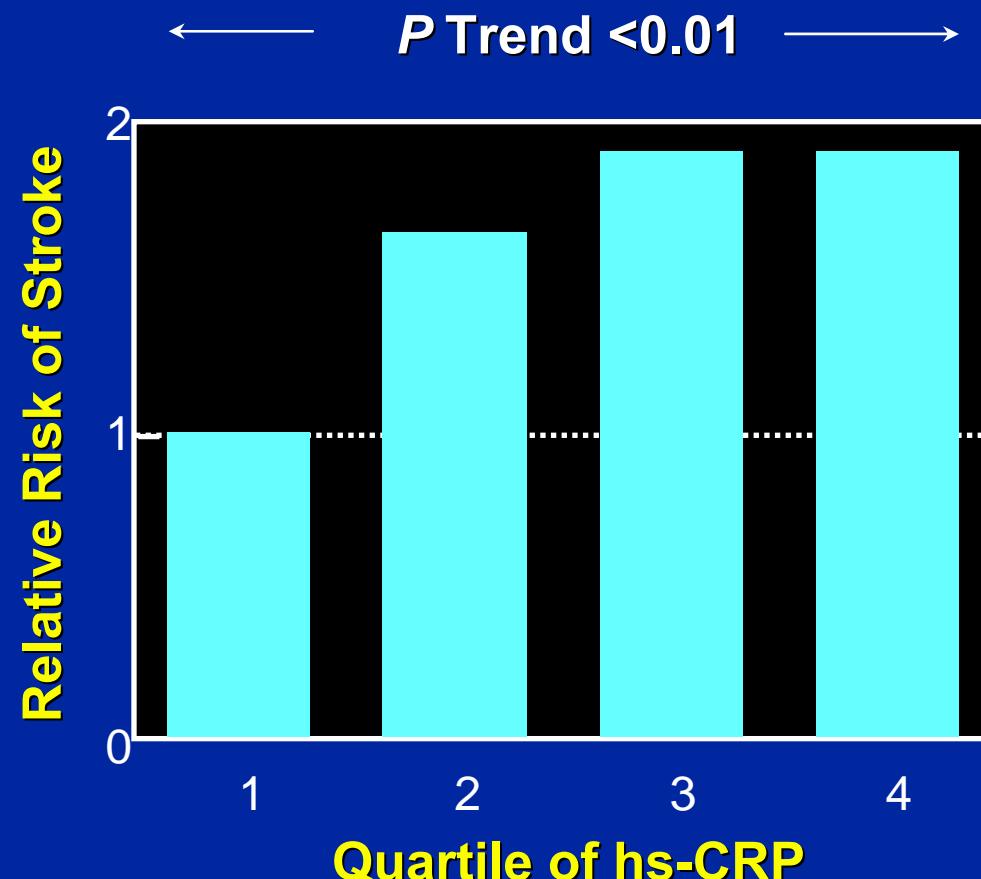
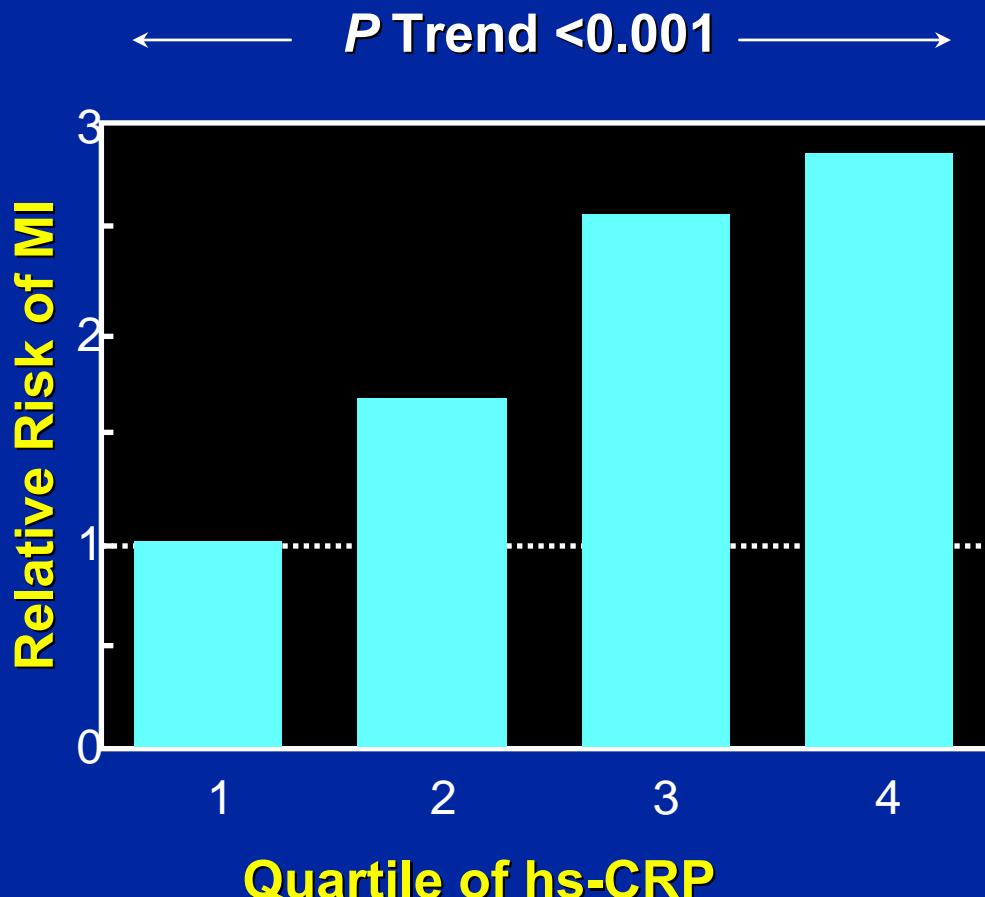
# Η hsCRP ΩΣ ΔΕΥΤΕΡΟΣ ΣΤΟΧΟΣ ΤΗΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΑΓΩΓΗΣ

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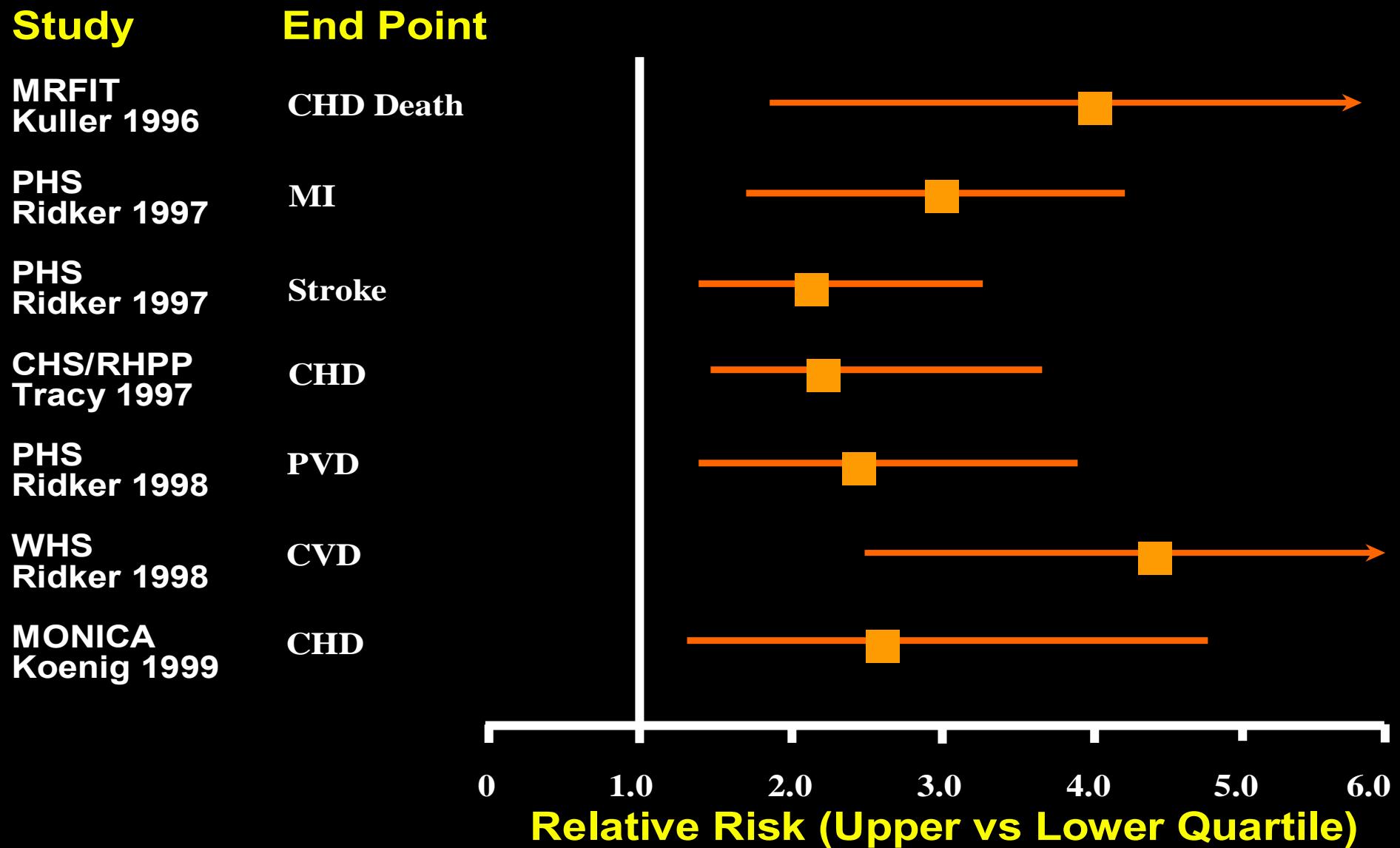
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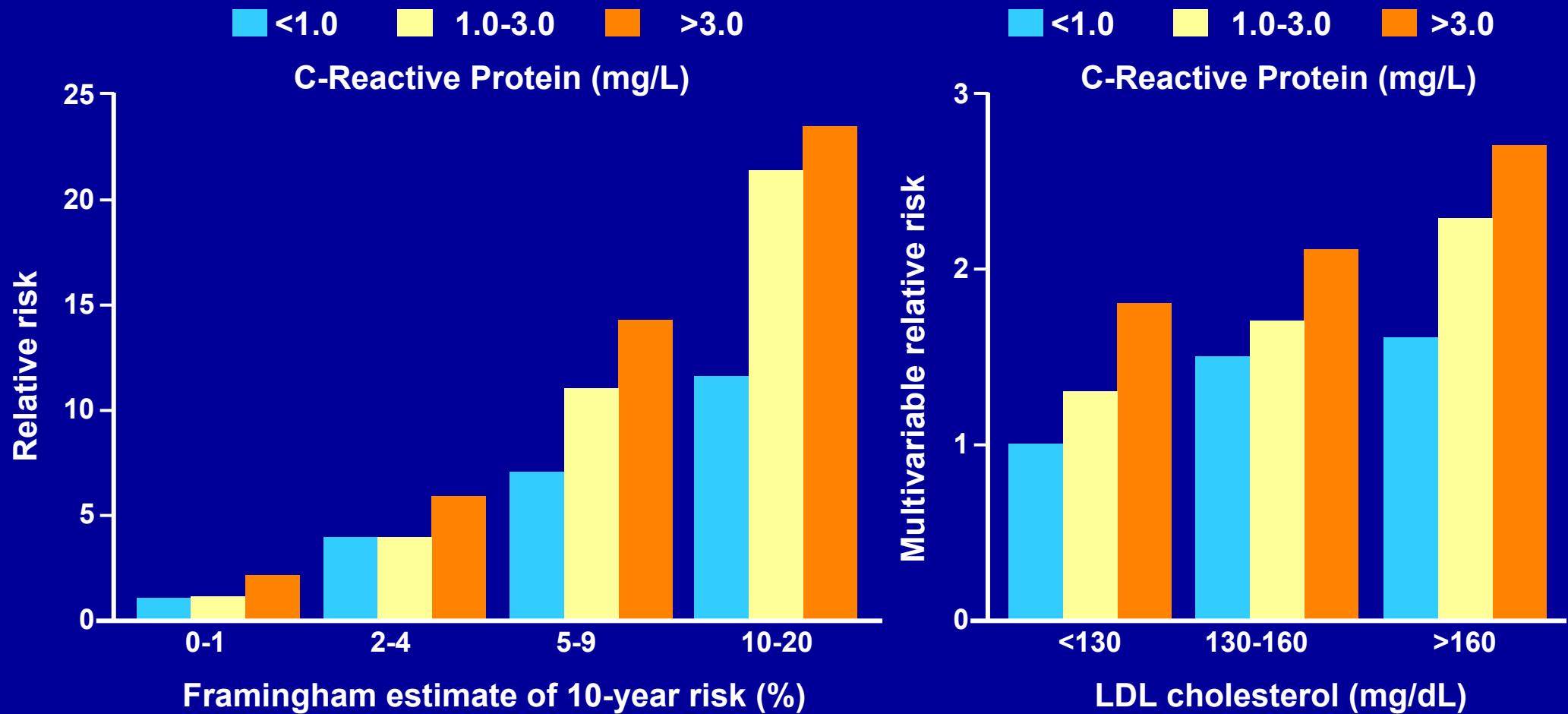
# hsCRP and Risk of Future MI and CVA in Apparently Healthy Men



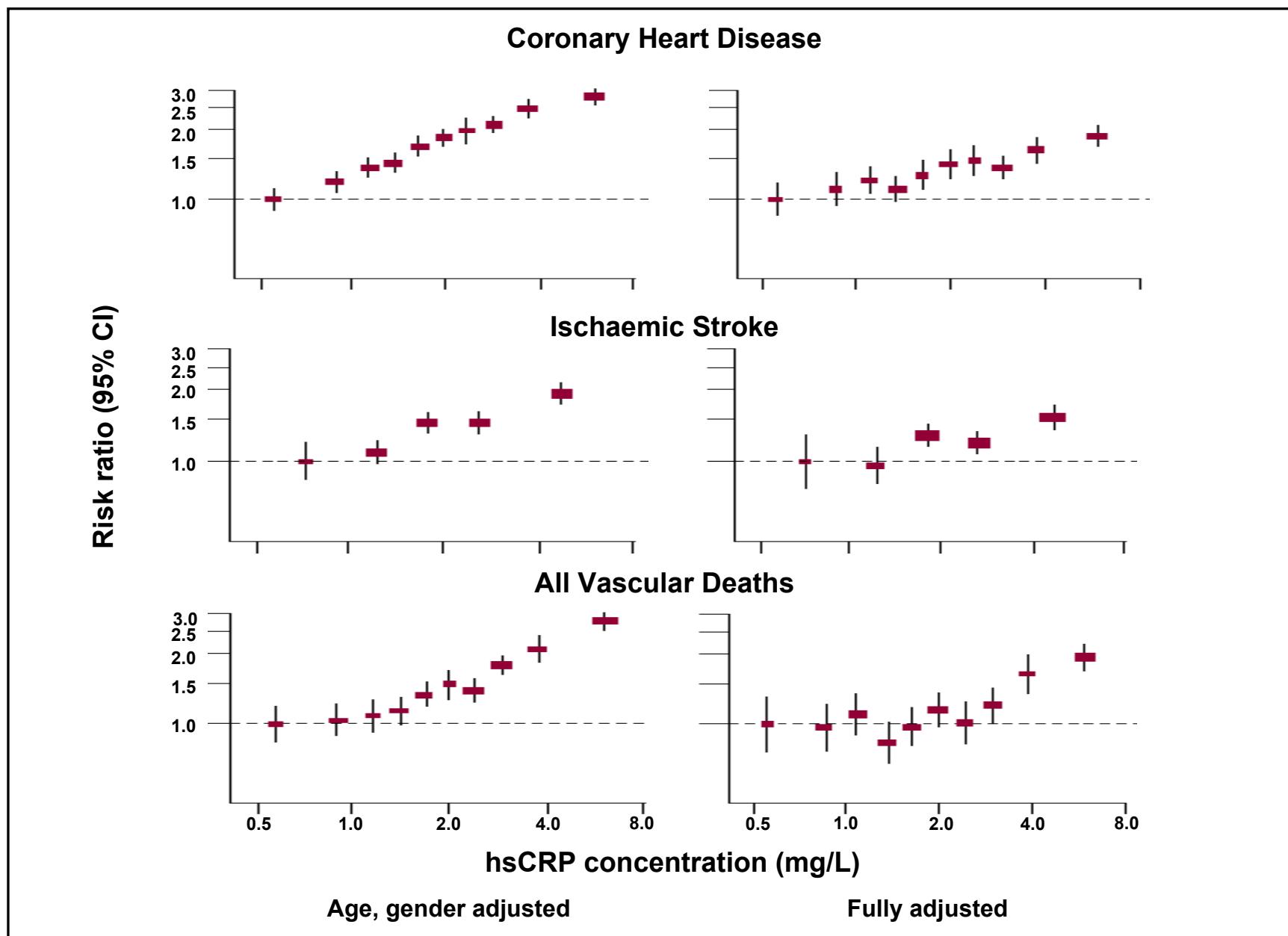
# HS - CRP AS A PREDICTOR OF CVD IN HEALTHY SUBJECTS



# hs-CRP Adds Prognostic Information at all Levels of LDL-C and at all Levels of the Framingham Risk Score

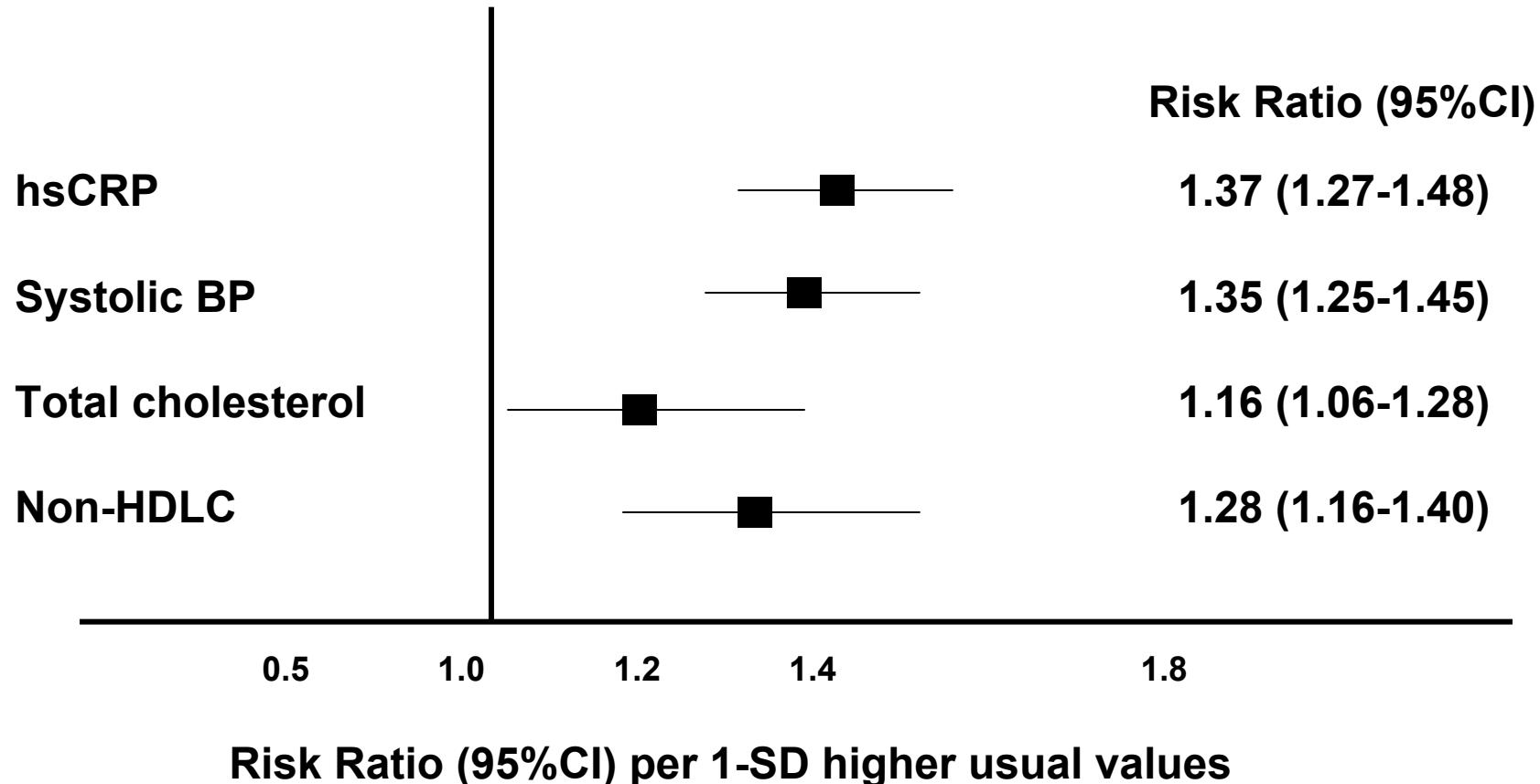


# C-reactive protein concentration and risk of cardiovascular events (n=160,309, 54 studies)



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

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



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

# Η hsCRP ΩΣ ΔΕΥΤΕΡΟΣ ΣΤΟΧΟΣ ΤΗΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΑΓΩΓΗΣ

❑ Η αύξηση της hsCRP είναι ανεξάρτητος παράγοντας κινδύνου ✓

❑ Η hsCRP προάγει την αθηρωμάτωση??

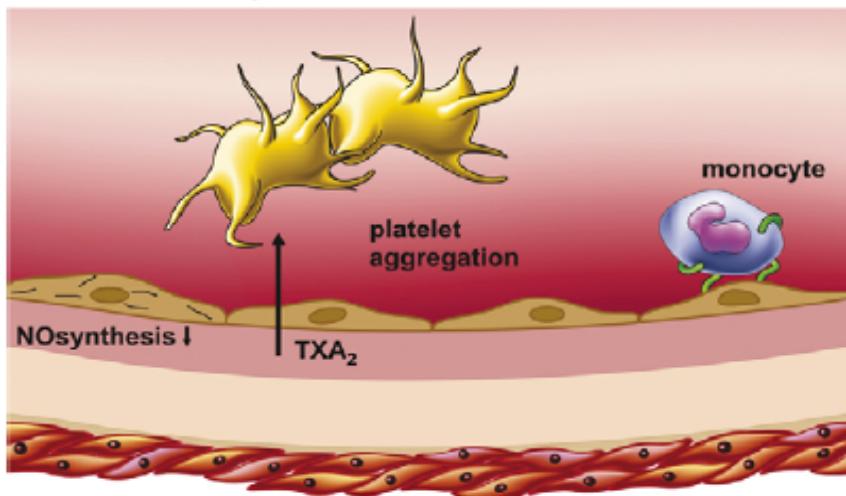
❑ Η μείωση της hsCRP → σημαντική μείωση των συμβαμάτων??



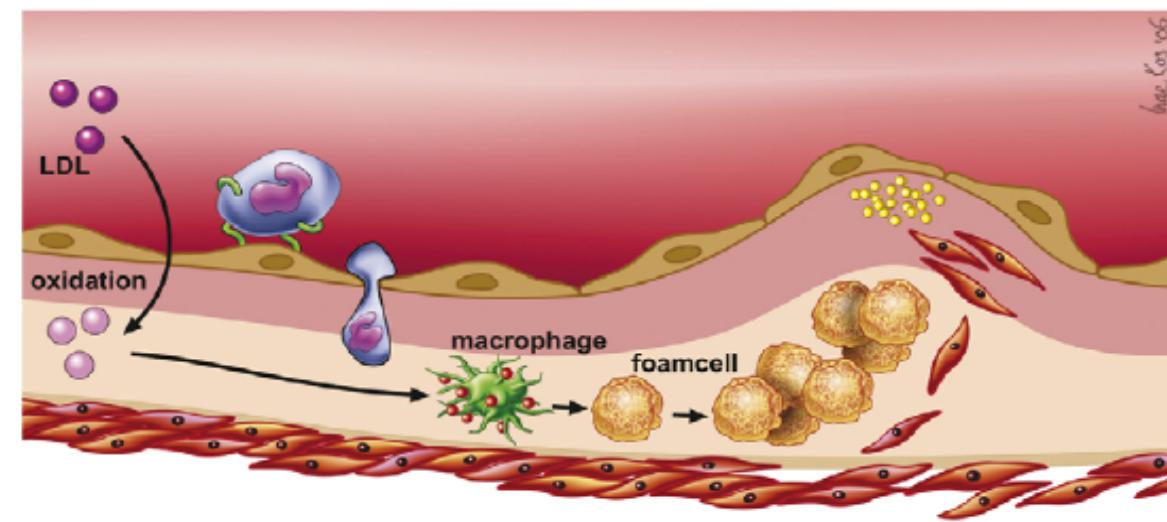


# CRP and atherogenesis: from fatty streak to clinical event

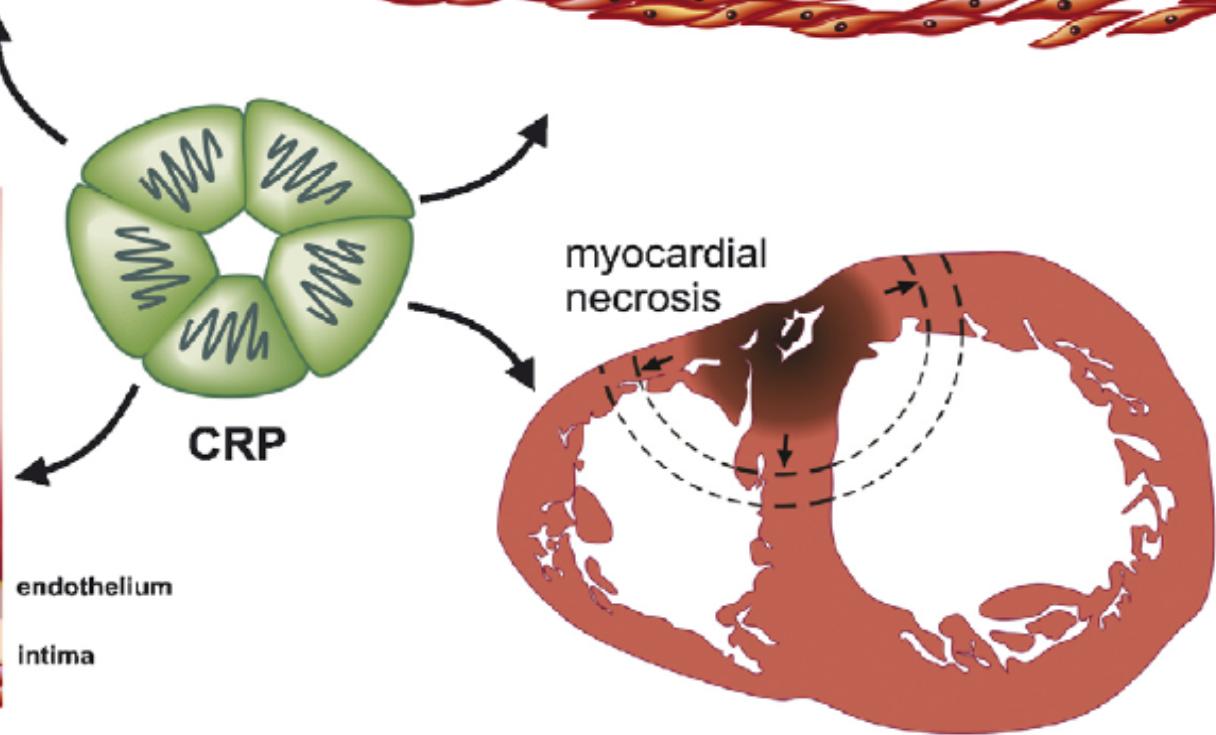
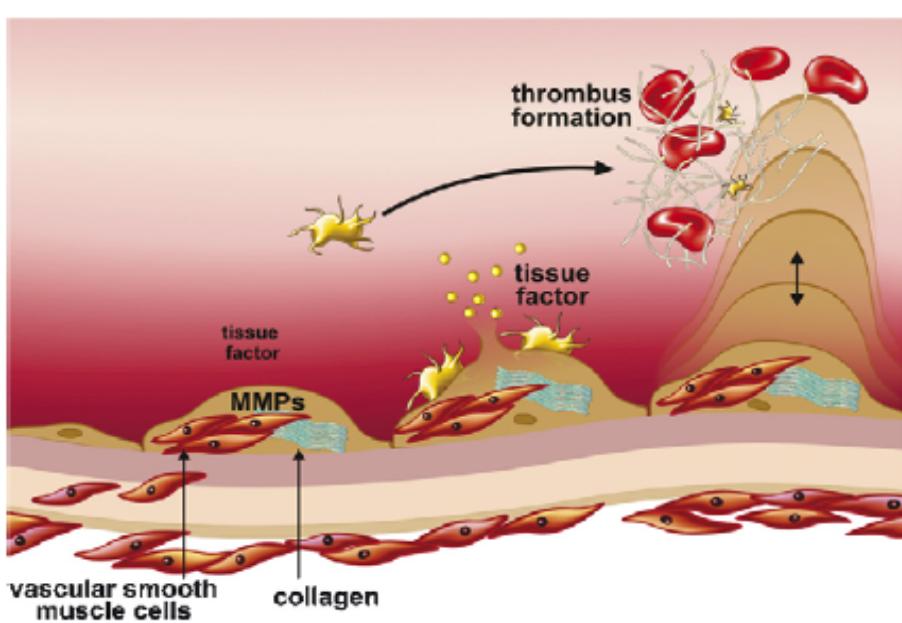
## endothelial dysfunction



## fatty streak



## plaque rupture



# Η hsCRP ΩΣ ΔΕΥΤΕΡΟΣ ΣΤΟΧΟΣ ΤΗΣ ΘΕΡΑΠΕΥΤΙΚΗΣ ΑΓΩΓΗΣ

❑ Η αύξηση της hsCRP είναι ανεξάρτητος παράγοντας κινδύνου ✓

❑ Η hsCRP προάγει την αθηρωμάτωση ✓?

❑ Η μείωση της hsCRP → σημαντική μείωση των συμβαμάτων??

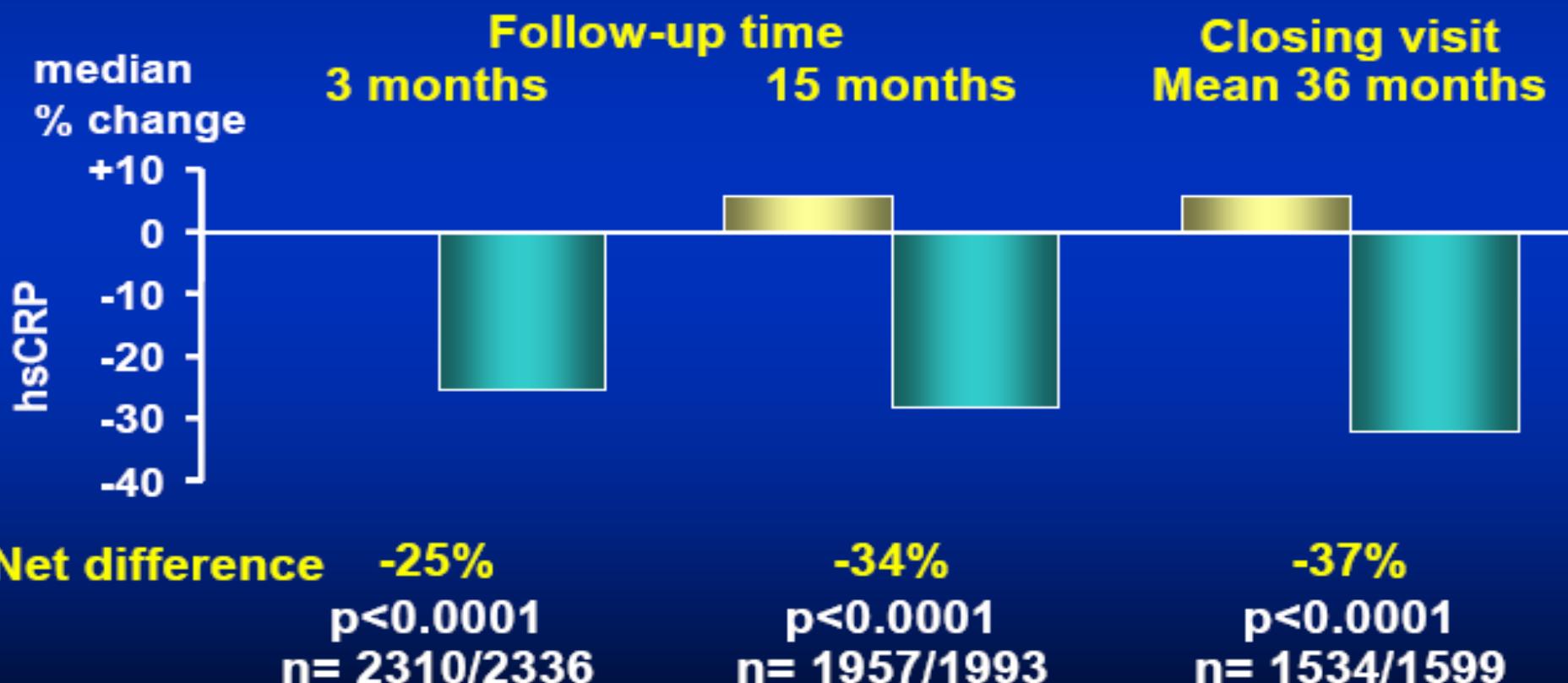
ΔΕΝ ΥΠΑΡΧΟΥΝ ΜΕΛΕΤΕΣ ΜΕ  
ΦΑΡΜΑΚΑ ΠΟΥ ΝΑ ΜΕΙΩΝΟΥΝ  
ΑΠΟΚΛΕΙΣΤΙΚΑ ΤΗΝ hsCRP

# Median hsCRP at Baseline and % Change During Follow-up

## Baseline median values

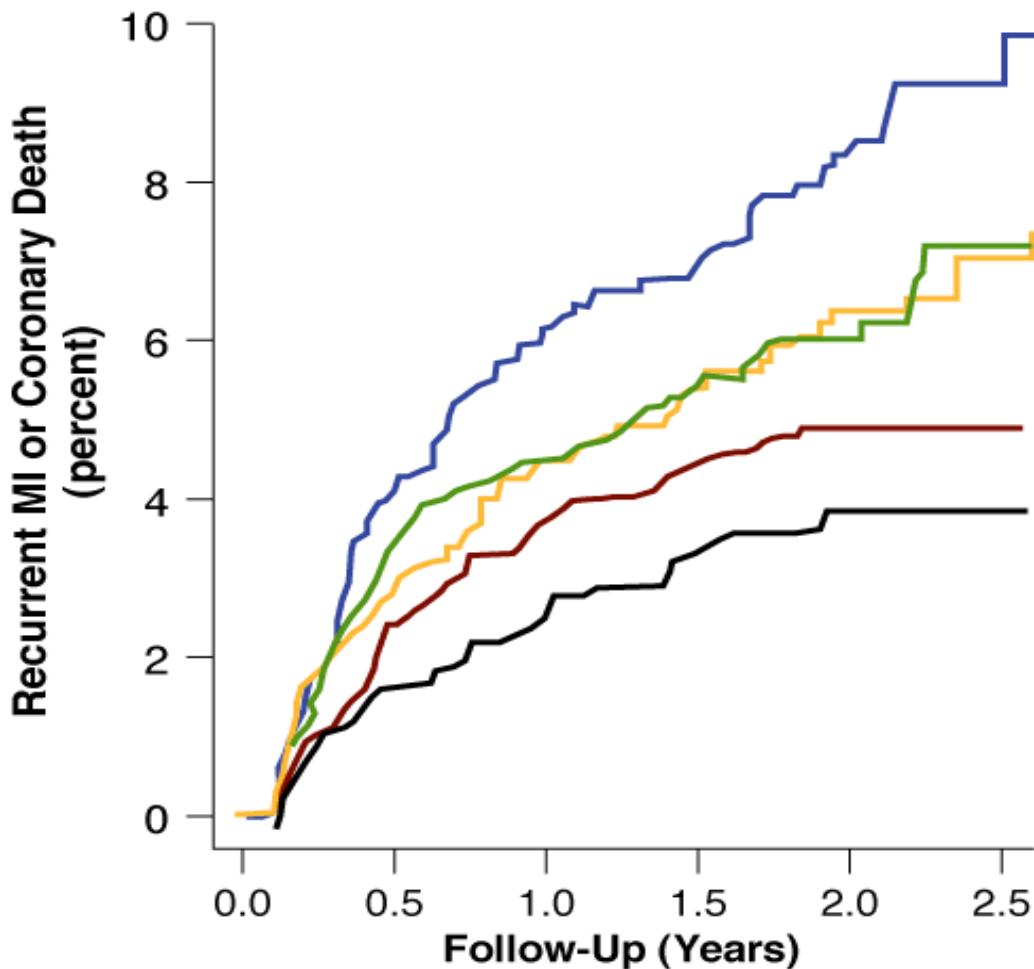
Placebo 3.50 mg/L

Rosuvastatin 3.50 mg/L





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



$\text{LDL} \geq 70 \text{ mg/dL}$ ,  $\text{CRP} \geq 2 \text{ mg/dL}$

$\text{LDL} \geq 70 \text{ mg/dL}$ ,  $\text{CRP} < 2 \text{ mg/dL}$

$\text{LDL} < 70 \text{ mg/dL}$ ,  $\text{CRP} \geq 2 \text{ mg/dL}$

$\text{LDL} < 70 \text{ mg/dL}$ ,  $\text{CRP} < 2 \text{ mg/dL}$

$\text{LDL} < 70 \text{ mg/dL}$ ,  $\text{CRP} < 1 \text{ mg/dL}$

Reproduced with permission from Ridker PM, Cannon CP, Morrow D, et al. C-Reactive Protein Levels and Outcomes after Statin Therapy. *N Engl J Med.* 2005;352:20-28. Copyright © 2005, Massachusetts Medical Association. All rights reserved.



Content Provided by the American College of Cardiology

# A to Z

# REVERSAL Rates of Progression According to the Change in LDL Cholesterol and CRP Levels

**Table 4.** Rates of Progression According to the Change in LDL Cholesterol and CRP Levels.\*

Subgroup	No. of Patients	Percent Atheroma Volume†			Total Atheroma Volume (mm <sup>3</sup> )†		
		Median	95% CI	Mean ± SD	Median	95% CI	Mean ± SD
Reduction in LDL cholesterol and CRP both greater than median	141	0.24 (-2.8 to 3.5)‡	-0.77 to 0.54	0.33±5.3	-1.98 (-3.0 to 10.8)‡	-6.26 to 3.67	-2.41±31.6
Reduction in LDL cholesterol greater than median, reduction in CRP less than median	106	0.81 (-2.0 to 4.8)	-0.32 to 1.81	1.62±4.7	2.06 (-12.8 to 21.5)	-3.26 to 6.41	4.04±28.7
Reduction in LDL cholesterol less than median, reduction in CRP greater than median	108	1.21 (-2.0 to 4.0)	-0.31 to 2.08	0.91±4.9	-1.04 (-18.6 to 22.5)	-6.78 to 8.74	1.42±29.2
Reduction in LDL cholesterol and CRP both less than median	141	1.82 (-1.5 to 5.1)	1.0 to 2.84	2.25±5.0	8.21 (-1.8 to 27.5)	0.40 to 13.05	7.49±27.5

\* CRP levels were not available for six patients at baseline or follow-up. The subgroups were formed on the basis of the median percent change in LDL cholesterol of -37.1 percent and the median percent change in CRP of -21.4 percent.

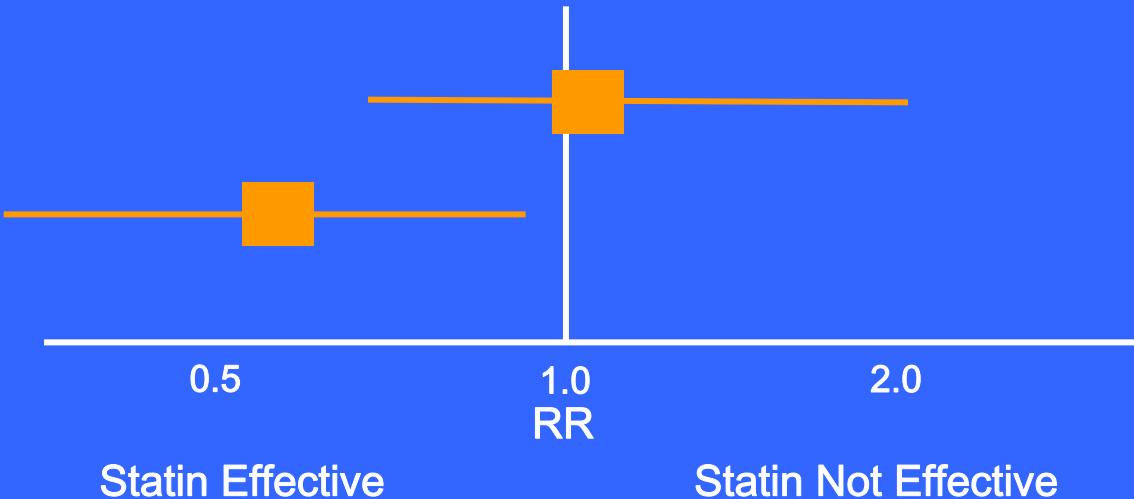
† Values in parentheses are interquartile ranges. Confidence intervals (CIs) are for the medians.

‡ P=0.001 for the comparison with the subgroup in which the reduction in the levels of both LDL cholesterol and CRP was less than the median reduction (by Wilcoxon's rank-sum test).

# AFCAPS/TexCAPS

## AFCAPS/TexCAPS Low LDL Subgroups

Low LDL, Low hsCRP



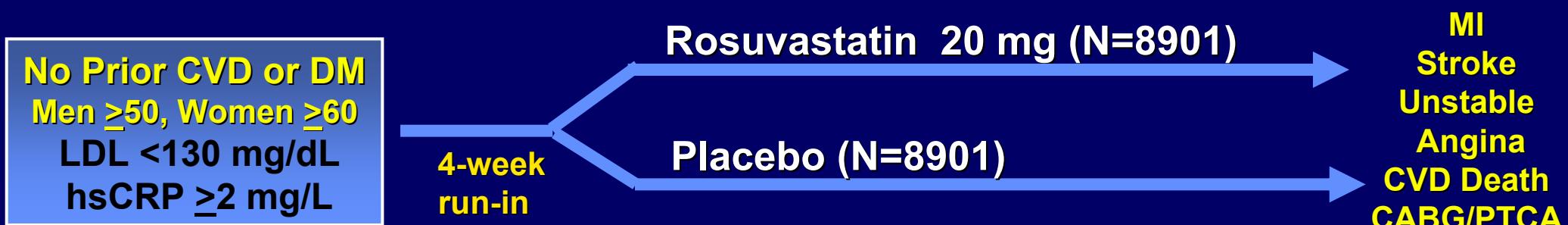
Low LDL, High hsCRP

However, while intriguing and of potential public health importance, the observation in AFCAPS/TexCAPS that statin therapy might be effective among those with elevated hsCRP but low cholesterol was made on a *post hoc* basis. Thus, a large-scale randomized trial of statin therapy was needed to directly test this hypotheses.

# JUPITER Trial Design

## 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

## Baseline Clinical Characteristics

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

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

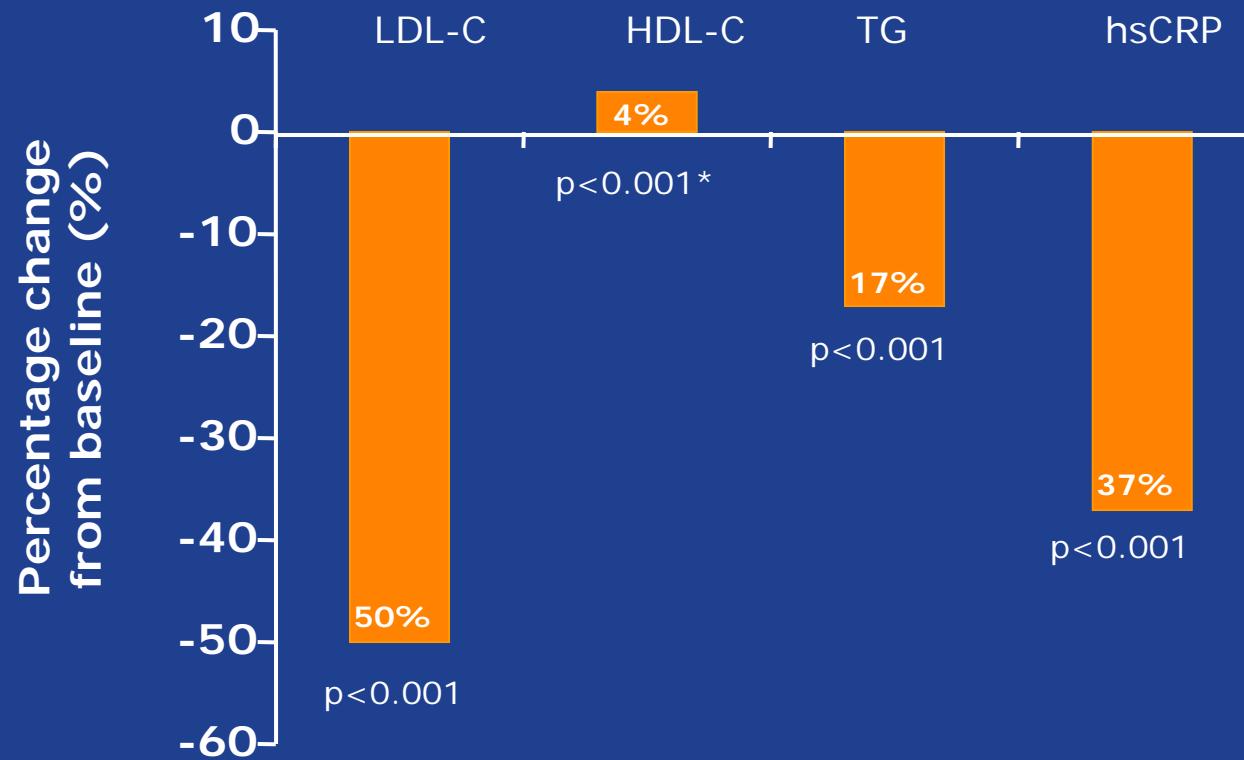
## Baseline Blood Levels (median, interquartile range)

	Rosuvastatin (N = 8901)	Placebo (n = 8901)
hsCRP, mg/L	4.2 (2.8 - 7.1)	4.3 (2.8 - 7.2)
LDL, mg/dL	108 (94 - 119)	108 (94 - 119)
HDL, mg/dL	49 (40 – 60)	49 (40 – 60)
Triglycerides, mg/L	118 (85 - 169)	118 (86 - 169)
Total Cholesterol, mg/dL	186 (168 - 200)	185 (169 - 199)
Glucose, mg/dL	94 (87 – 102)	94 (88 – 102)
HbA1c, %	5.7 (5.4 – 5.9)	5.7 (5.5 – 5.9)

All values are median (interquartile range). [ Mean LDL = 104 mg/dL ]

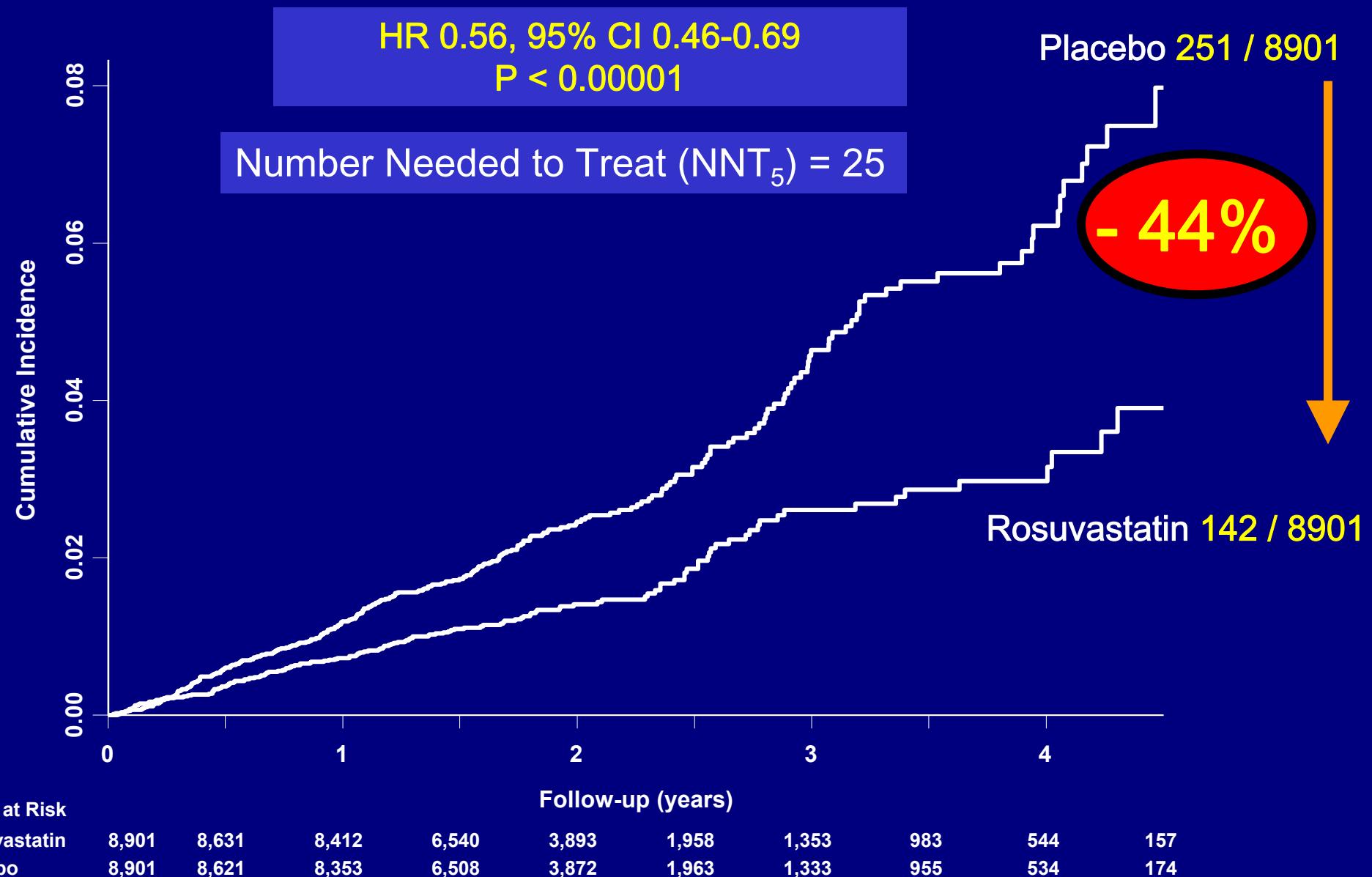
# JUPITER

Effects on LDL-C, HDL-C, TG and hsCRP at 12 months;  
*Percentage change between rosuvastatin and placebo*

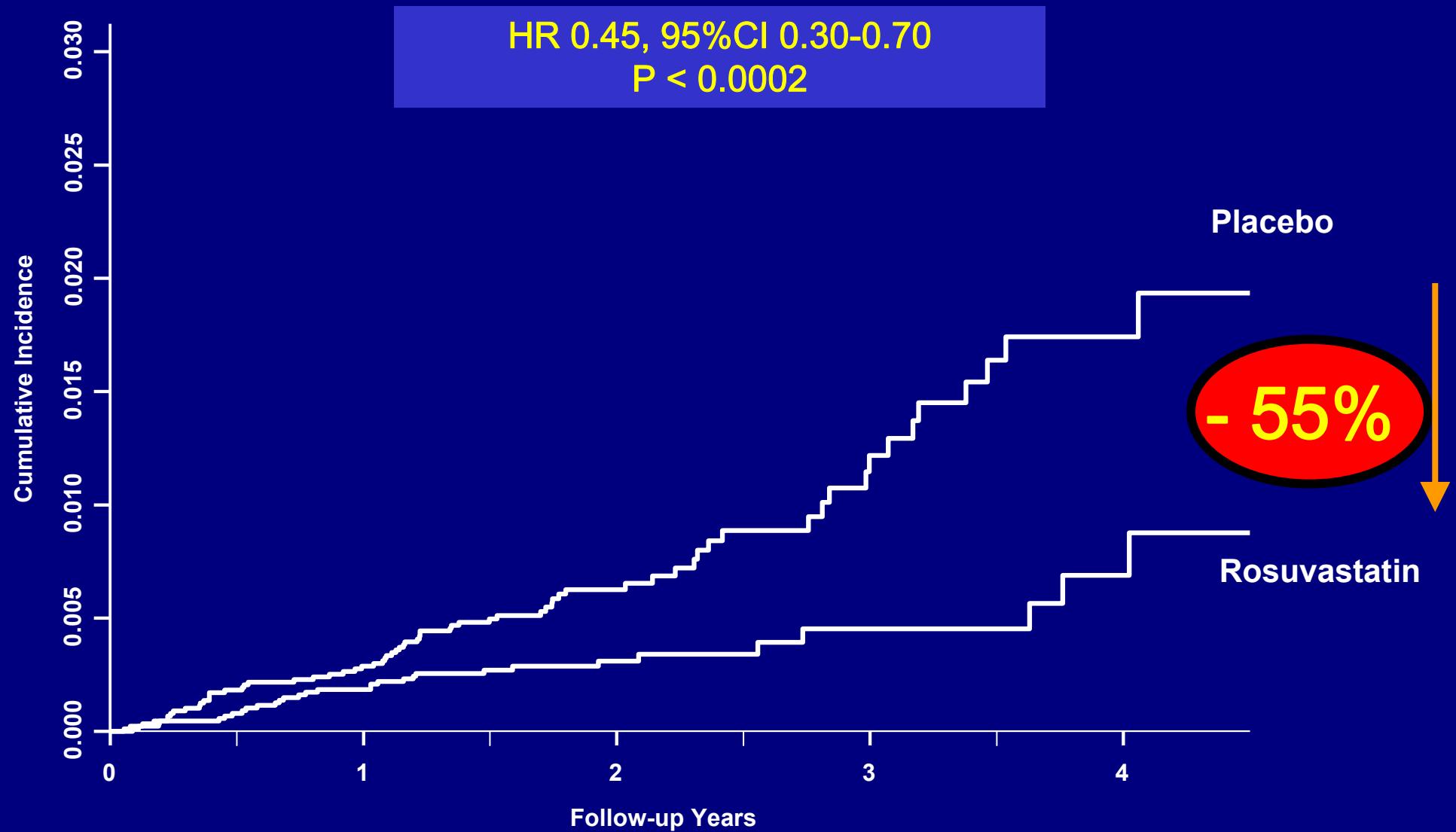


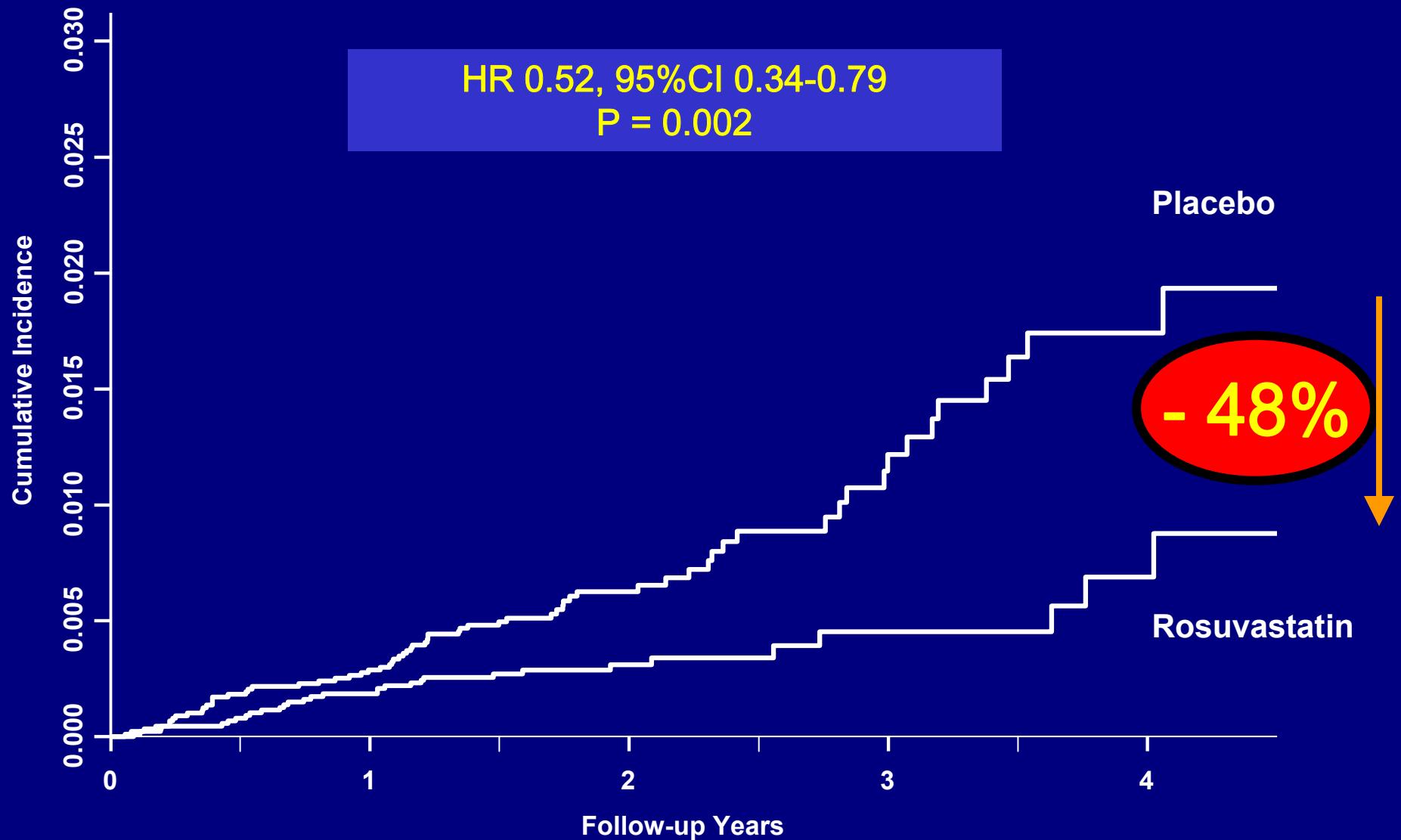
\*P-value at study completion (48 months) = 0.34

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

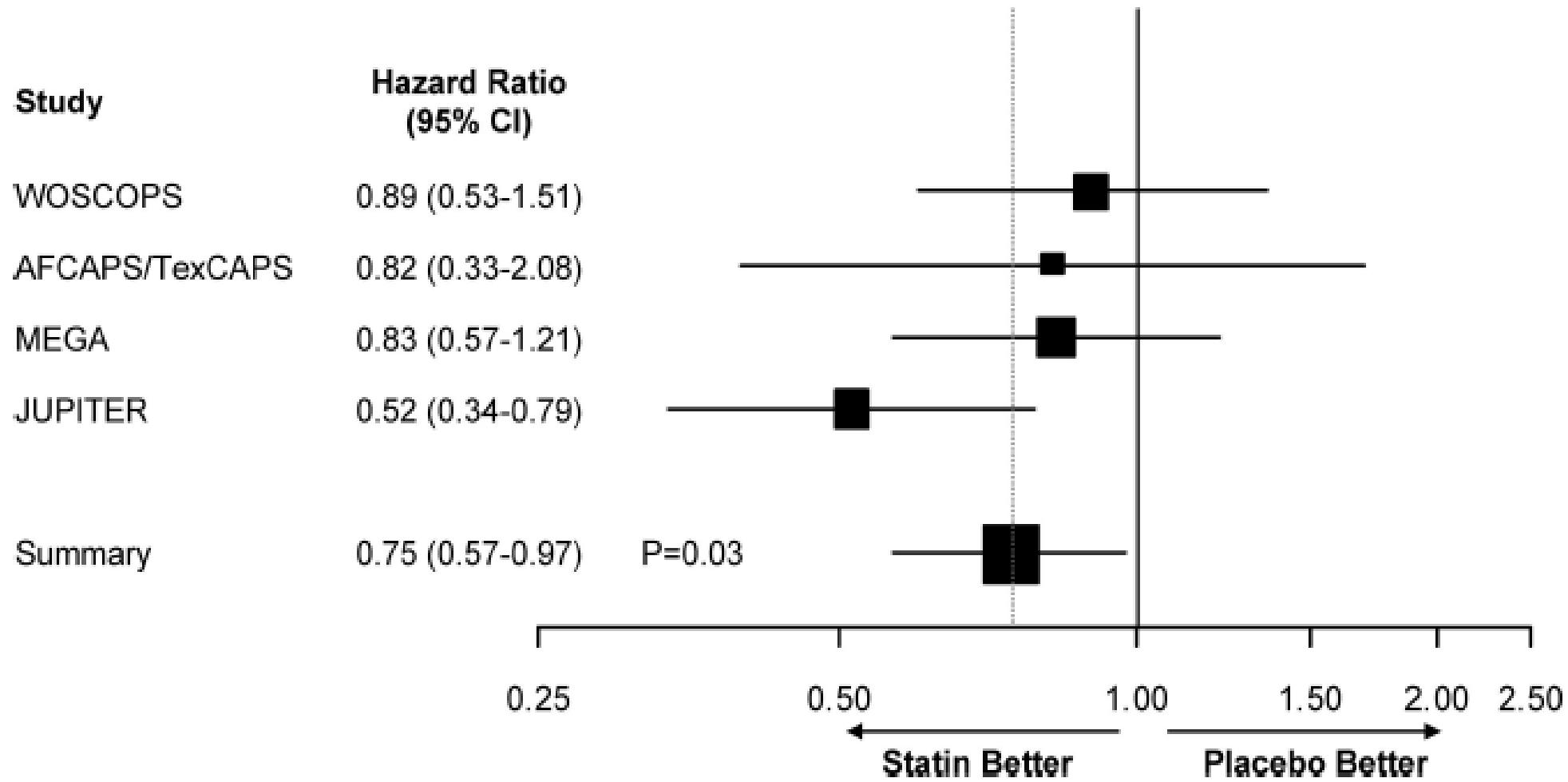


## Fatal or Nonfatal Myocardial Infarction

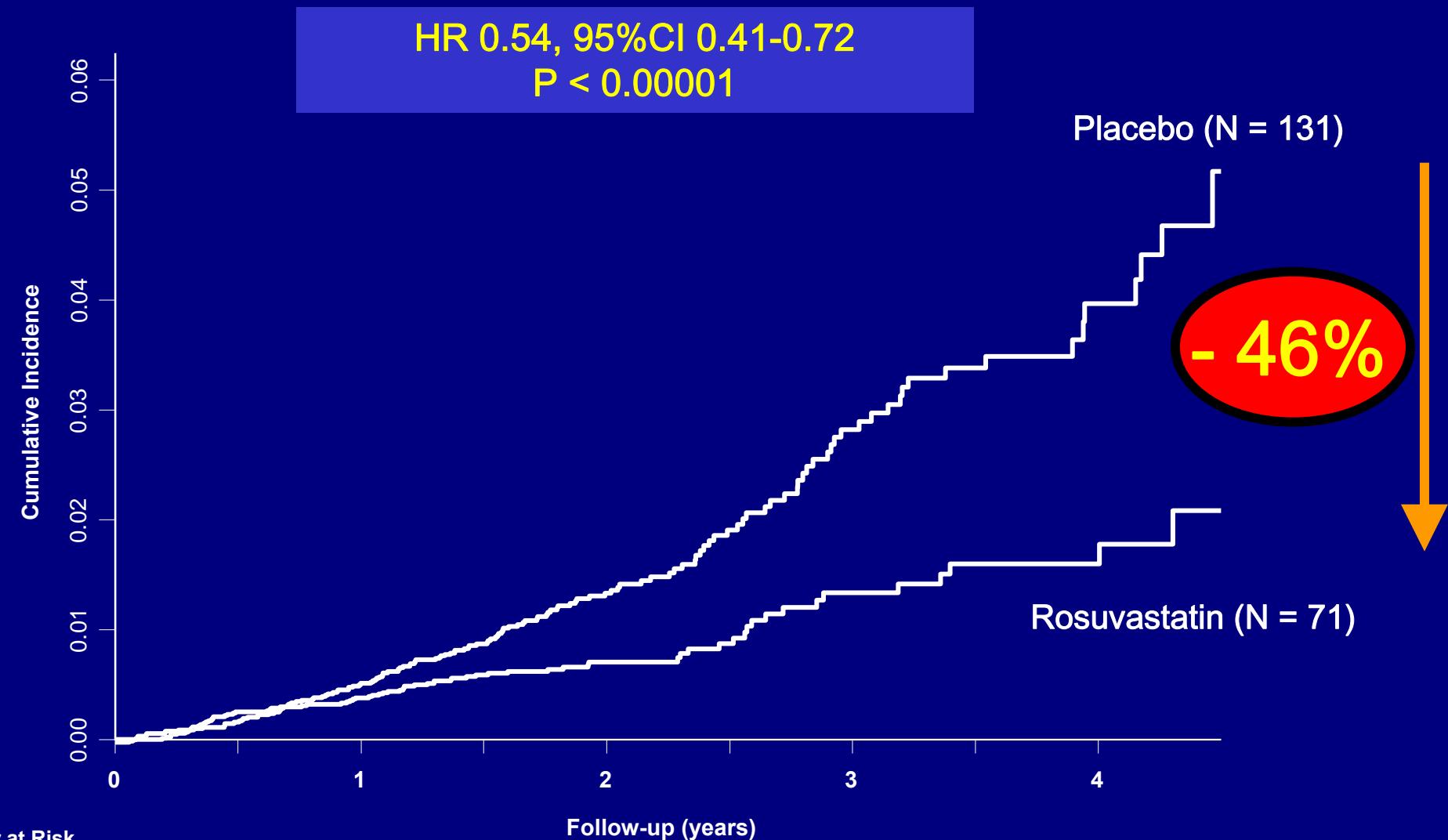




# Risk of Stroke in Four Statin Primary Prevention Trials



## Bypass Surgery / Angioplasty



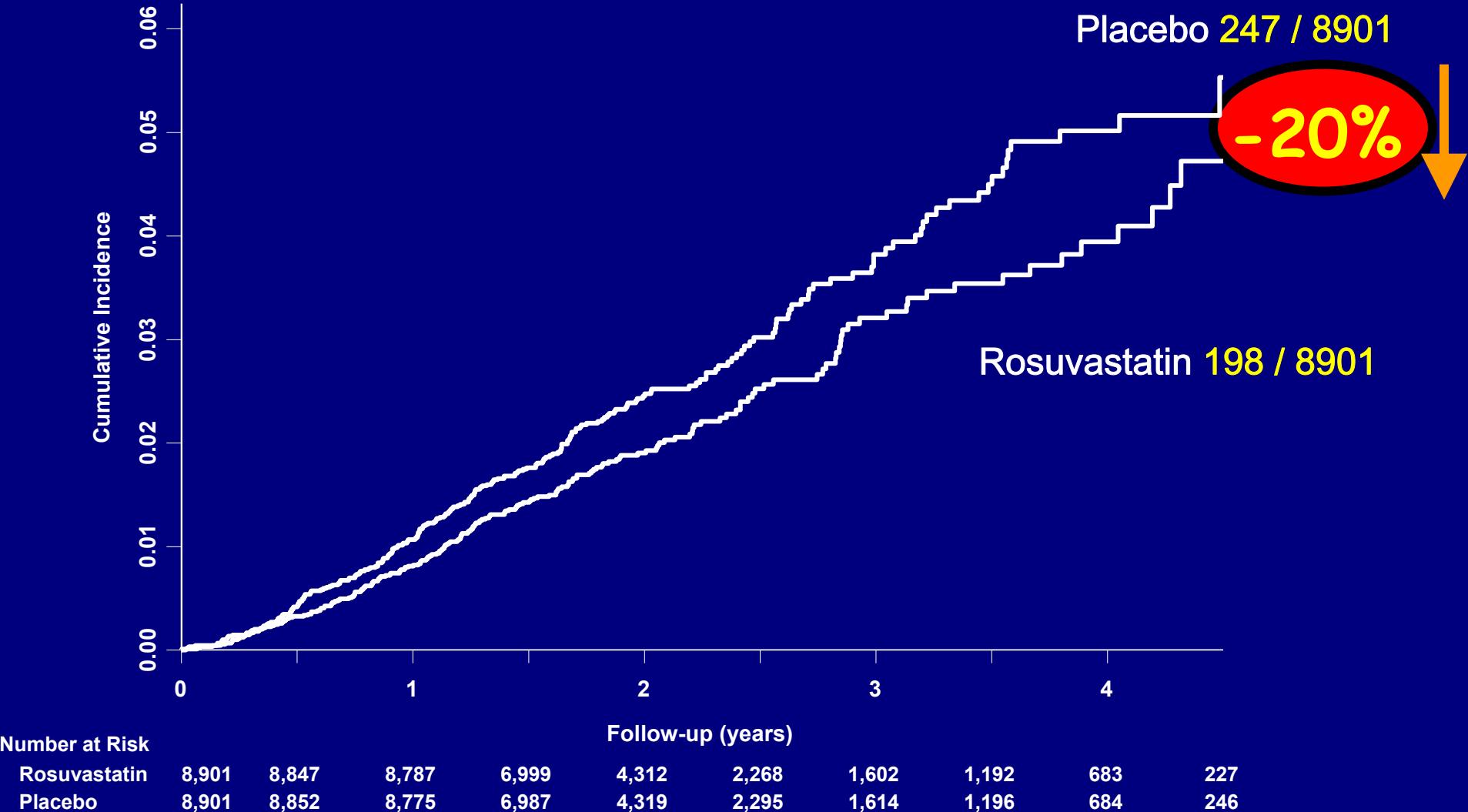
## Number at Risk

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	

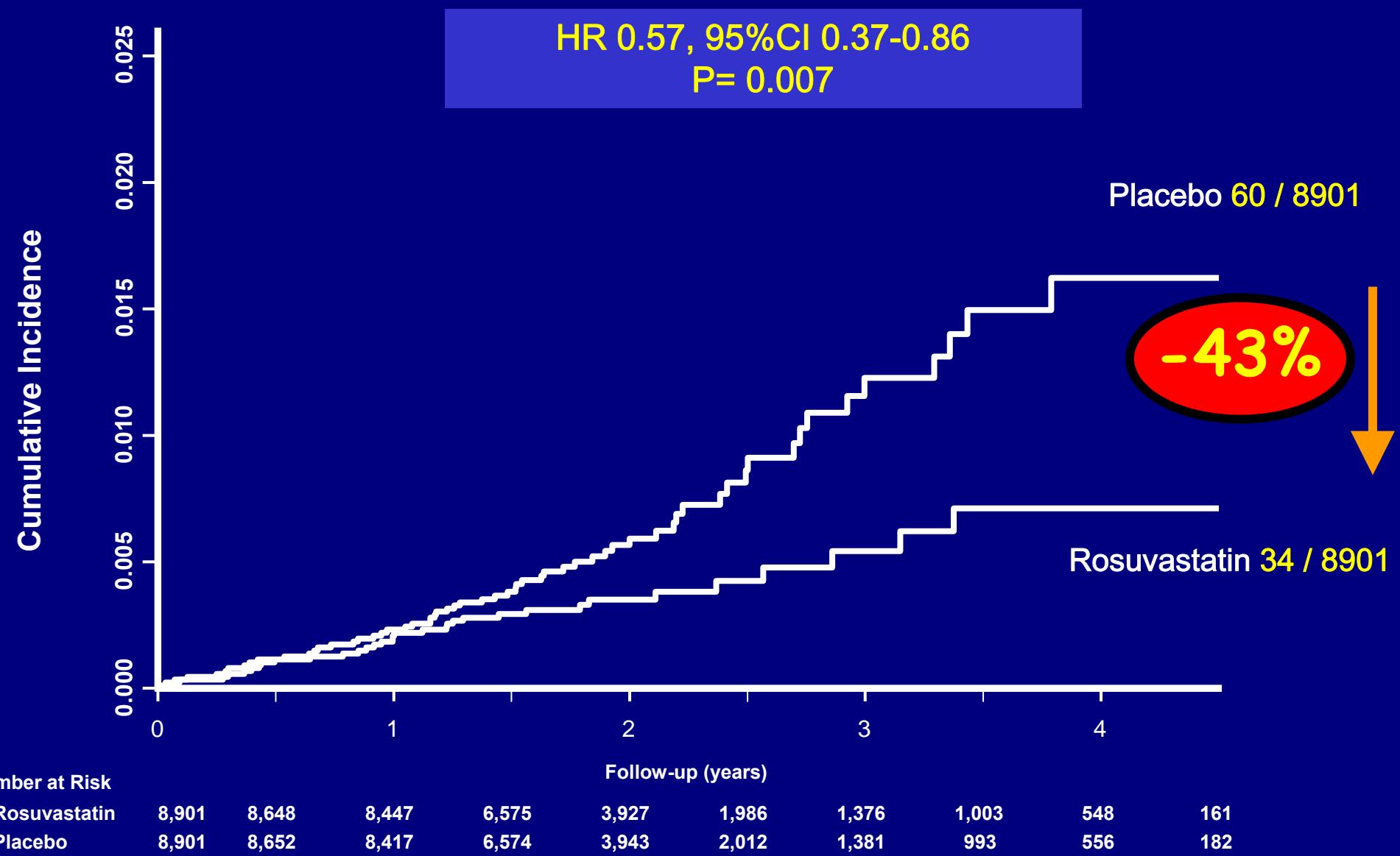
## Secondary Endpoint – All Cause Mortality

HR 0.80, 95%CI 0.67-0.97

P= 0.02

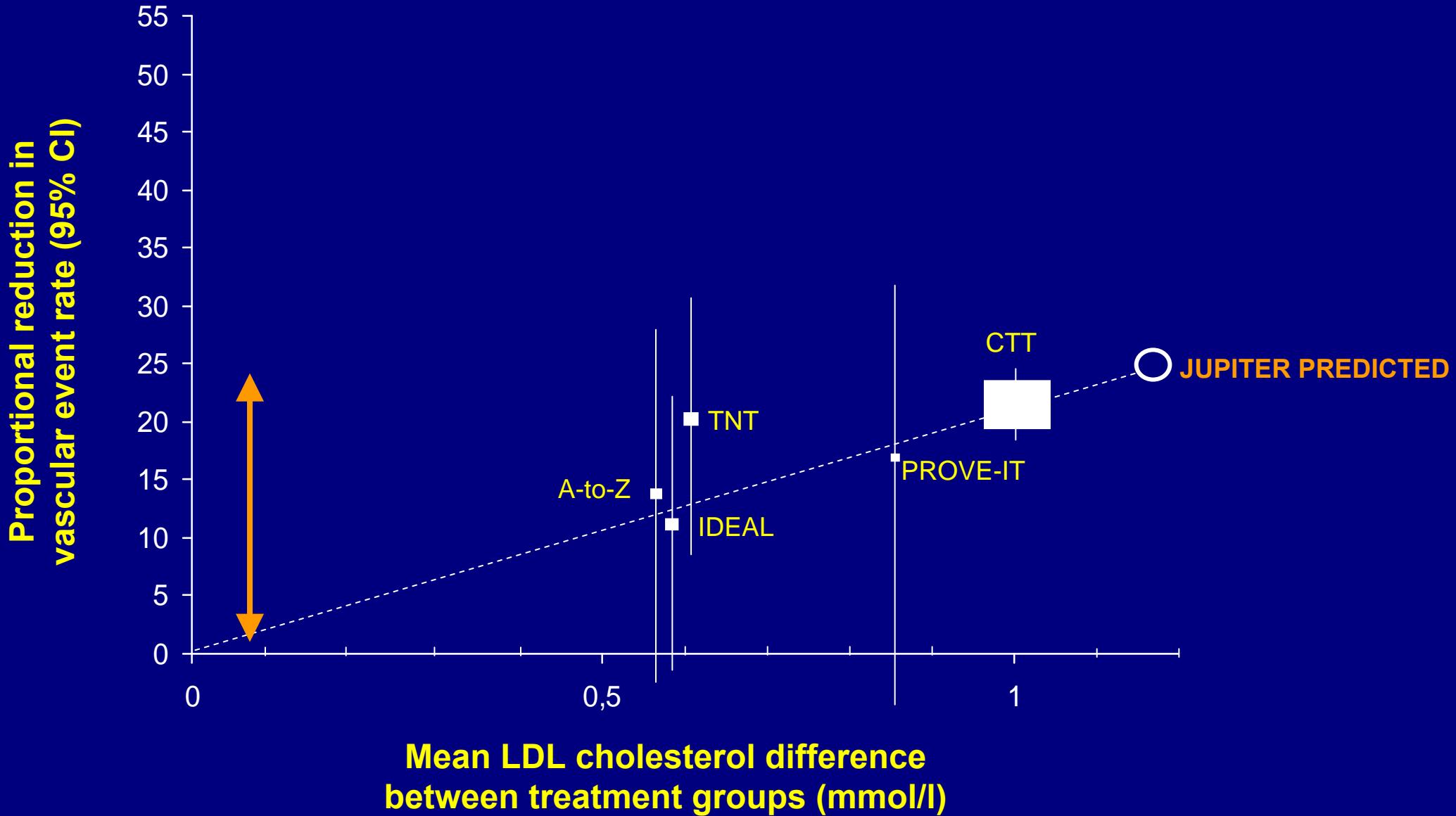


## Total Venous Thromboembolism

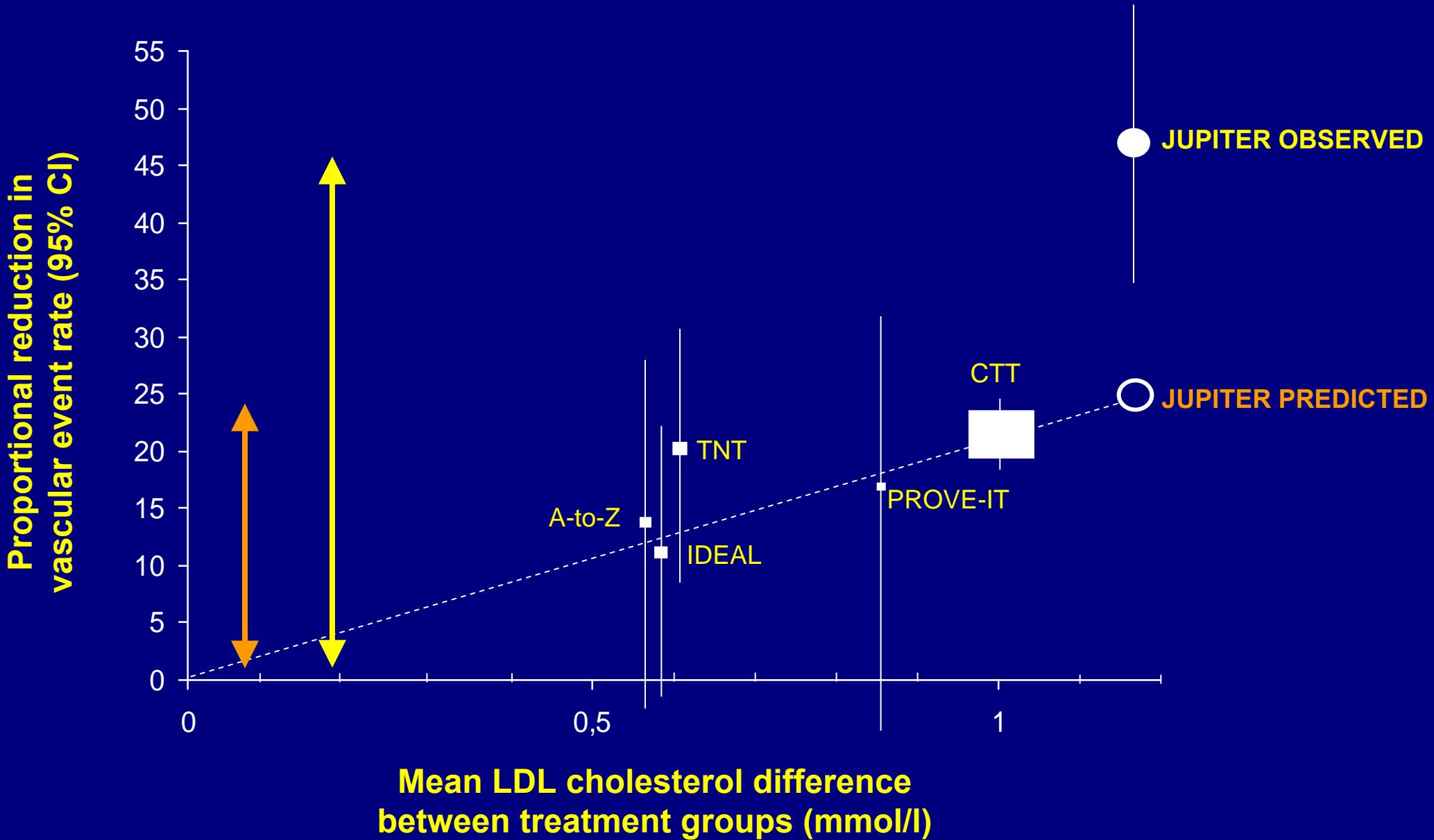


Είναι η μείωση της LDL-C ή  
της hsCRP που συνέβαλαν στο  
τελικό αποτέλεσμα?

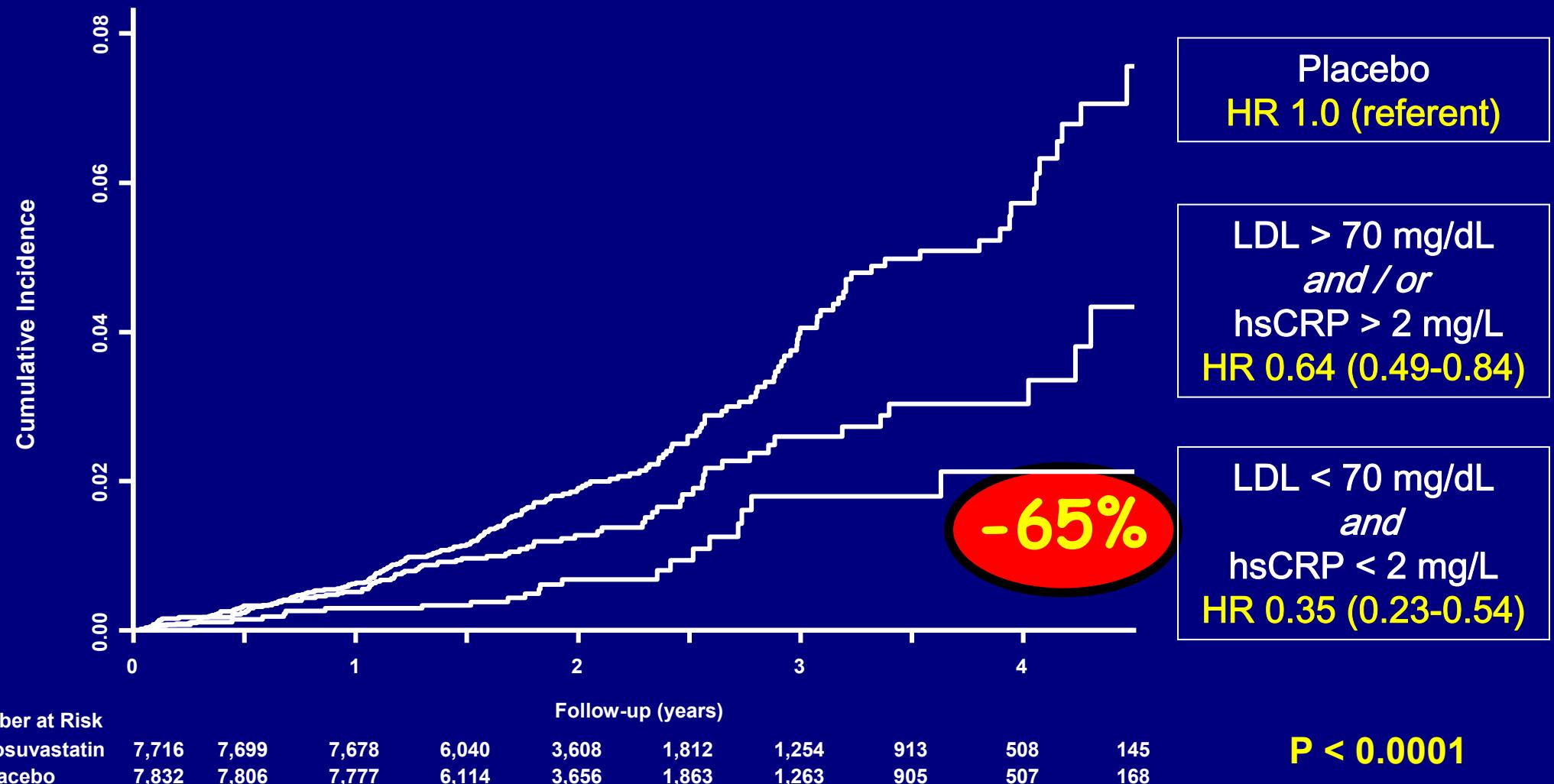
## Predicted Benefit Based on LDL Reduction vs Observed Benefit



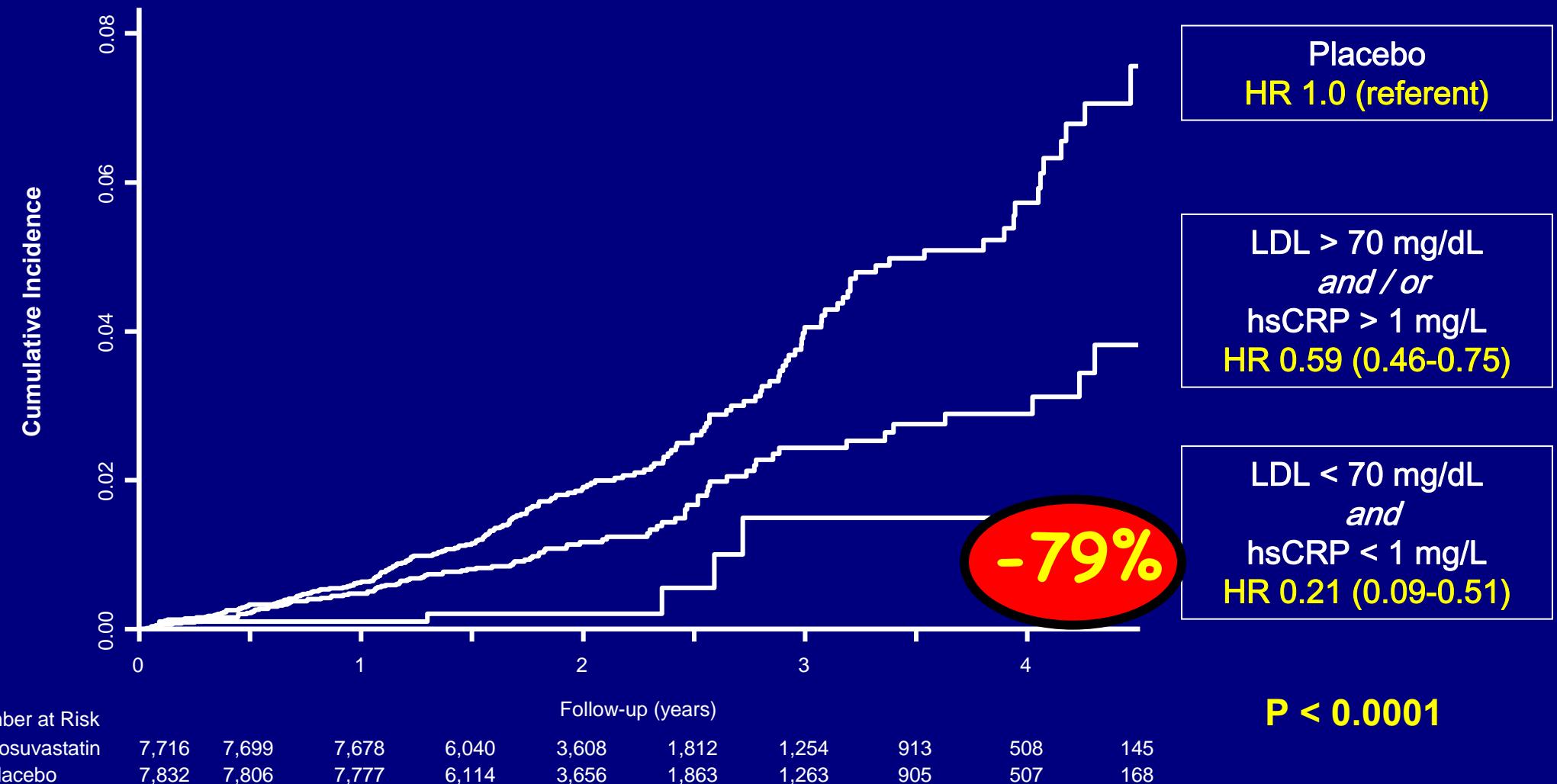
## Predicted Benefit Based on LDL Reduction vs Observed Benefit



## Dual Target Analysis: LDLC&lt;70 mg/dL, hsCRP&lt;2 mg/L



## Dual Target Analysis: LDLC&lt;70 mg/dL, hsCRP&lt;1 mg/L



# FDA APPROVAL (9/2/2010)

ROSUVASTATIN NOW INDICATED TO  
REDUCE THE RISK OF MI, STROKE AND  
REVASCULARAZATION:

- IN SUBJECTS >50 YEARS (MEN) OR >60 YEARS (WOMEN)
- WITH NORMAL LDL-C BUT hsCRP >2.0 mg/L
- + 1 ADDITIONAL RISK FACTOR (high blood pressure, low HDL-C, smoking, or a family history of premature heart disease)

-Specific inhibition of CRP is feasible with a small molecule synthetic compound [1,6-bis(phosphocholynine)-hexane]

-This compound produced smaller infarct sizes in rats



Πρέπει να μετράμε τα  
επίπεδα της hsCRP κατά τη  
διάρκεια της θεραπείας με  
στατίνη και τι θα κάνουμε αν  
τα βρούμε αυξημένα?

CARE, AFCAPS, PROVE IT, A to Z, Reversal, JUPITER

## Does Correct Use of Statin Therapy Require Evaluation for *both* LDLC and hsCRP?

---

- 1. LDL-C is a strong, independent predictor of future CV events**
- 2. Statins Lower LDL-C**
- 3. The level of LDL-C achieved after starting statin therapy predicts recurrent event rates (ie “lower is better”)**

- 1. hsCRP is a strong, independent predictor of future CV events**
- 2. Statins Lower hsCRP**
- 3. The level of hsCRP achieved after starting statin therapy predicts recurrent event rates (ie “lower is better”)**

Dual Goals for Statin Therapy :  
LDL-C < 70 mg/dL and hsCRP < 2 mg/L

1. Εντατικοποίηση των υγιεινοδιαιτητικών μέτρων (απώλεια βάρους, άσκηση, διακοπή καπνίσματος, υγιεινή διατροφή)
2. Εντατικοποίηση της Θεραπείας με στατίνη-αλλαγή σε ισχυρότερη στατίνη

# 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% <b>RRS &gt;20%</b>	<80 mg/dL or 50% reduction	Class I Level A
Moderate	FRS 10-19% RRS 10-19% LDL >135 mg/dL TC/HDLC >5.0 <b>hsCRP &gt;2 in men &gt;50 yr women &gt;60 yr</b>	<80 mg/dL or 50% reduction	Class II A Level A
Low	FRS <10%	<190 mg/dL	Class II A Level A
Secondary Targets		TC/HDLC <4, non HDLC <135 mg/dL <b>hsCRP &lt;2 mg/L, TG &lt;150 mg/dL, ApoB/A &lt;0.8</b>	

**ΣΤΟΧΟΣ ΤΗΣ ΑΓΩΓΗΣ:**

Η ΜΕΙΩΣΗ ΤΗΣ hsCRP

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